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THE TOXIC EFFECTS OF TRI-ORTHO-CRESYL PHOSPHATE ON THE NERVOUS SYSTEM

AN EXPERIMENTAL STUDY IN HENS

BY

J. B. CAVANAGH

From the Department of Pathology, Guy's Hospital Medical School, London

While the clinical effects of tri-ortho-cresyl phosphate (T.O.C.P.) on the nervous system of man are now widely known from the papers of Ter Braak (1931), Sampson (1938, 1942), Aring (1942), Staehelin (1942), and of Hunter, Perry, and Evans (1944), the process by which degeneration of the peripheral nerves and the long tracts of the spinal cord is brought about is less well understood. From their original studies Smith and Lillie (1931) concluded that T.O.C.P. was " a specific myelin poison " and that it probably exerted this action by virtue of its solubility in lipoid substances. Aring (1942) from his observations on late cases of T.O.C.P. poisoning in man also believed that this substance had a specific affinity for nervous tissue, but he was unable to suggest a satisfactory mechanism by which nerve and tract degeneration was brought about. One year earlier, however, a new line of approach to the problem was opened up by Bloch's (1941) demonstration that T.O.C.P. inhibited the cholinesterase of horse serum, and it appeared reasonable for him at that time to suggest that the paralysis due to T.O.C.P. might possibly be the result of inhibition of cholinesterase at the myoneural junctions. This view, however, became untenable for it was found that although T.O.C.P. inhibited both serum cholinesterase and tributyrinase, it was ineffective not only against other enzymes such as serum phosphatase and pancreatic lipase (Hottinger and Bloch, 1943) but also against the true cholinesterase of red blood cells and motor end-plates (Mendel and Rudney, 1944). Nevertheless distinction between the two forms of cholinesterase had been thus emphasized. As details of the distribution in the body of serum or pseudocholinesterase came to be worked out, particularly in the nervous system, where it was found to be in greatest amount in the white fibre tracts and in the peripheral nerves (Burgen and Chipman, 1951 ; Ord and Thompson, 1952) it came to be thought possible that it might in some way be concerned with the metabolism of myelin. This was supported by Koelle's (1950) histochemical demonstration that the enzyme was located in the Schwann and supportive glial cells of the nervous system rather than in the conductive elements. Despite the growing amount of information on the localization of this enzyme and its activity *in vitro*, there are as yet no direct indications as to its function *in vivo* or upon what substrates it is active. Largely due to these important gaps in our knowledge there is still much uncertainty as to the part played by inhibition of pseudocholinesterase in the production of the demyelinating lesions in T.O.C.P. intoxication, and this uncertainty is aggravated by striking species differences in the readiness with which changes in the nervous system can be produced by different cholinesterase inhibitors. This lack of correlation between enzyme inhibition and biological effect has been remarked upon by Barnes and Denz (1953) who have cast some doubt upon whether inhibition of pseudocholinesterase by these agents is in fact as important a factor in producing nervous tissue damage as has been hitherto believed.

Turning to the histological aspects of T.O.C.P. intoxication, it is remarkable to find that, although studies by many authors of the changes in both man and experimental animals have yielded the information that demyelination regularly occurs in the peripheral nerves and in certain tracts of the spinal cord, little attention has been paid to the mode of onset of these changes or to determining whether they are primary or merely secondary to degeneration in the axis cylinder. In view of the discrepancies briefly outlined above between the functional disorder and the biochemical changes, a closer and more detailed examination of the pathological process as it affects the nervous system would seem to be warranted, since, for further

progress, an answer must be sought as to whether the demyelination is primary or not. If it is primary, then some additional support will be provided for the hypothesis that pseudocholinesterase resident in the glial and Schwann cells plays some part in the nourishment of the myelin sheath. If, on the other hand, myelin degeneration is secondary to axis cylinder degeneration then it would be more reasonable to look for some biochemical effect of T.O.C.P. upon the neuron itself in order to explain the occurrence of the lesions.

Observations on Paralytic Changes after the Administration of T.O.C.P.

Although the main features of the functional disturbances of the nervous system that follow the administration of T.O.C.P. have been noted by other workers, since this study is particularly concerned with correlating the earliest structural changes with the appearance of functional disorder, a brief note on the present findings would not be out of place. Hens were exclusively used because of the uniform manner with which they react to a single oral dose, and because the effects upon the pseudocholinesterase of both serum and nervous tissue have been closely studied in these animals by Earl and Thompson (1952). Birds of mixed breed were employed aged from 6 months to 2 years, and the T.O.C.P. (Geigy Pharmaceutical Laboratory, Ltd.) was administered in doses of 1 ml./kg. body weight by means of a rubber-tipped glass pipette introduced into the oesophagus.

The birds were examined and exercised daily, and although in the days immediately following poisoning they usually appeared to be in good health, it was observed that in fact there was a steady drop in weight of about 50 g. each day, which figure represented 2 to 3% of their initial weight. The weight loss continued for six to eight days but thereafter with the onset of paralytic symptoms it became less marked and a slight gain in weight was in general noted in the subsequent weeks. It is not clear whether this early loss of weight was the result of anorexia or of some other factor. The crops were always found to be distended with food when opened at necropsy.

The earliest evidence of damage to the nervous system began to appear in a few birds on the eighth day, though more generally on the ninth and tenth days. This was manifested by an unwillingness to walk and when made to do so they tired easily and would prefer to squat. After exercise a decided broadening and clumsiness of the gait could be elicited. When repeatedly made to fly for a short distance, although the first landings were executed normally, subsequently they became more and more clumsy and unsteady during the first few steps after landing. Invariably on the day following these first signs of incipient paresis overt weakness and clumsiness were evident even without previous exercise. The feet would slap heavily on the floor, were clumsy and irregular in their action and were widely spread to maintain balance. During the subsequent four or five days the legs became progressively more weakened until the bird was unable to stand. Examination during this period showed that the ankle jerks were uniformly depressed and the legs were hypotonic. Power was severely reduced in the ankle and knee movements but the upper parts of the limbs were still able to perform quite strong actions though these were poorly coordinated. Changes in sensation were difficult to elicit. In the remainder of the body, although the wings were sometimes noticeably weakened, they were never affected to the same degree as the legs. No impairment of the head and tail righting reflexes was ever observed.

By the end of the first fortnight, therefore, most birds were severely paralysed in the legs, but a few were still able to stand and in these ataxia was conspicuous. Once the condition had reached this stage there was little evidence of progression of the functional damage; the birds, however, frequently did poorly and failed to gain weight. Not infrequently they died unaccountably during the third and fourth week after poisoning. This last event, it was found, could be avoided without materially affecting the extent and severity of the paralysis by reducing the dose of T.O.C.P. to 0·75 or 0·5 ml./kg., and birds on these doses after an initial setback during the onset of the nervous damage gained weight and maintained good general health. With a dose of 0·25 ml./kg. only minimal functional changes in the nervous system could be discerned. Long-term studies of the regenerative capacity of the peripheral nerves after paralysis were not undertaken, but in view of the absence of gross damage to the anterior horn cells of the lumbo-sacral cord a certain amount of recovery of function would be predicted at least in the peripheral nervous system.

Methods

The birds were sacrificed by decapitation at various times from the third day onwards, particular attention being paid to the period immediately before and during the onset of the paralysis. After the skin had been stripped off, each sciatic nerve was exposed in turn from the trochanter of the femur to the ankle joint and portions from both distal and proximal regions were allowed to adhere to perforated card without shrinkage and dropped into 1% osmic acid to fix for 48 hours. Pieces adjacent

to these and from other parts of the nerve were similarly treated but fixed in formol-saline. The brachial nerve was taken in many instances, but chief attention was paid to the sciatic nerve and its branches. The brain and spinal cord were exposed and then allowed to fix for 48 hours in formol-saline before being dissected out together with posterior root ganglia at several levels. Blocks of muscle from foot, leg, and thigh were taken in many instances, but other non-nervous tissues were not systematically examined except with the naked eye.

The peripheral nerves that had been fixed in osmic acid were dissociated in glycerine, washed, and mounted in glycerine jelly. By this method it was judged that minimal distortion of the myelin sheaths had been incurred and at the same time quite considerable lengths of individual fibres, sometimes including four or five consecutive nodes of Ranvier, could be readily examined. Similar dissociated preparations of nerve fixed in formol-saline and stained with sudan black B were also examined for comparison. Frozen sections of both nerves and of spinal cord were stained with sudan black B and with the Smith-Quigley iron-haematoxylin method for myelin sheaths. Paraffin-embedded material from proximal and distal regions of the sciatic nerves and from different regions of the spinal cord and brain-stem, in many cases both in longitudinal and in transverse section, were stained routinely with haematoxylin and eosin and by the method of Glees and Marsland (1952) for axis cylinders. This last method was found to be particularly simple to execute and very constant in its results. The metallic methods of Cajal and of Hortega were employed as the occasion required. For degenerating myelin the Swank-Davenport technique was exclusively employed, the blocks after treatment being embedded in paraffin and sectioned at 10 μ. These were counterstained either with safranin or with haematoxylin and eosin.

Changes in the Peripheral Nerves

Myelin Sheaths.—No undoubted degenerative changes are evident in the myelin sheaths of the peripheral nerves during the first week following the administration of T.O.C.P. The internodal regions of the sheaths are smooth and regular and with polarized light the clefts of Schmidt-Lantermann are everywhere readily visible. Except for some irregularity on either side of the nodes of Ranvier, present in both osmic acid and in formol-fixed material, the significance of which is not clear, there is no hint of the changes that were to be observed during the course of the second week and thereafter.

From the eighth or ninth day there began to appear, first in a few fibres and later in increasing numbers, early signs of the myelin breaking up. This began with the formation of globules of various sizes out of the myelin sheath more or less simultaneously throughout the whole length of the internodes (Fig. 1). At the same time there was loss of the normal anisotropic reaction of the sheath to polarized light. The onset of myelin disintegration, therefore, appeared to resemble very closely the onset of the changes of Wallerian degeneration that follow interruption of the axis cylinder, and the subsequent alterations of the lipoid globules were of the same character. On following individual fibres in dissociated preparations it was apparent that this change was not confined to particular internodal segments, but was continuous along the whole length of the individual fibres studied. All fibres, however, were not affected in this way at the same time and from the twelfth day onwards sheaths in different stages of disintegration were encountered lying beside unaffected fibres. It is difficult, indeed, to state when exactly the onset of degeneration ceased, but by the end of the third week the changes in the affected sheaths were all in a more or less advanced state and there was little evidence of any fresh changes. It is noteworthy that fibres of large diameter were predominantly involved and those of medium size were less conspicuously

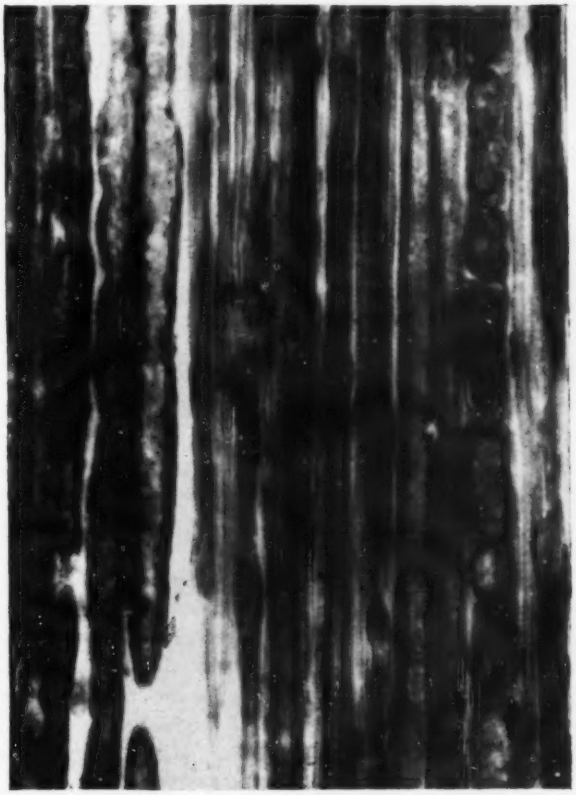

FIG. 1.—Sciatic nerve 14 days after poisoning, showing one sheath in a moderately early stage of degeneration and another just beginning to break up into globules. Frozen section stained with sudan black B. × 830.

affected, with the result that predominantly muscular branches of the sciatic nerve were more severely damaged than those passing to the extremity that contain chiefly cutaneous sensory fibres (Fig. 2). On the other hand, studying a nerve at different levels, such as the anterior tibial, shows that there is a greater amount of degenerating tissue distally than there is proximally, a finding that fits in with the view that these changes are Wallerian in character and are extending peripherally in the expected manner.

Axis Cylinders.—As with the myelin sheath, no definite change can be appreciated in the axis cylinders until the beginning of the second week, when *pari passu* with the myelin sheath changes, individual axons begin to show ballooning, nodularity, and fragmentation. These affected fibres are scanty on the eighth and ninth days but thereafter they become more numerous. Again it is evident that there are a greater number of damaged fibres in the distal parts of the nerves than there are more proximally (Figs. 3 and 4) and different fibres do not show the same stages of degeneration at any one time. With the idea in mind that degeneration might be occurring earlier in the distal parts of the limb than in the proximal, a search was made in the muscles of the lower leg, but in no instance was there found any more severe degree of nerve degeneration than could be accounted for by the amount of change higher up in the nerve, a finding in keeping with the probable secondary nature of the degeneration.

Changes in the Cells of Schwann.—Before the onset of the phase of secondary degeneration, that is during the first week after poisoning, no visible alteration in the appearances of the Schwann cells could be discerned, but following the disintegration of the axon and the myelin sheath the cells of the affected fibre begin to proliferate and become conspicuous after the twelfth to the fourteenth day after poisoning (Fig. 5). At about the same time macrophages were evident in the affected fibres, but foam cells did not make their appearance to any conspicuous degree until about the twentieth day onwards. Droplets of scharlach-staining lipids were not visible until the fourth week after poisoning. It is apparent therefore that the normal process of cell proliferation occurs here but on a reduced scale as it does following nerve section and no evidence is found to suggest that T.O.C.P., at any rate for the time periods studied here, affects cell proliferation in the nerve changes that this substance produces.

Changes in the Spinal Cord and Brain-Stem

The Fibre Tracts.—Examination of Swank-Davenport preparations of the spinal cord from the twelfth day onwards after poisoning shows substantially the same distribution of degenerative changes that have been noted by other authors. The ventral tract of large, heavily myelinated fibres is severely affected in the thoracic and lumbosacral regions (Fig. 9) and is less extensively involved in the cervical regions, where the dorso-lateral tracts (spino-cerebellar tracts) are predominantly attacked. Degeneration in the latter can be traced along the lateral aspects of the medulla into the cerebellum. Degeneration is also present in the upper thoracic and cervical regions in the posterior columns in a narrow band on either side of the dorsal septum. The tract can be traced up to the cervico-medullary junction at which point the fibres end in association with the secondary sensory neurons as in other species. There is never the same degree of change in this last funiculus that is found in either of the other two. Scattered fibres in the other regions of the white matter occasionally, but not constantly, also show evidence of disintegration of myelin with this technique.

In the brain-stem tract degeneration is not so constant as it is in the cord, but not infrequently individual fibres can be picked out in the dorsal cochlear commissure and in the medial longitudinal fasciculus (Fig. 6) while a degenerating fibre is occasionally to be found in the midbrain. It is probably of significance that both the medial longitudinal fasciculus and the fibres of much of the vestibulo-cochlear system are heavily myelinated and that they are tracts of considerable importance in the reflex pathways of the balancing mechanisms that are so highly developed in birds.

Silver-impregnated preparations show that, in all the regions described, where there is myelin fragmentation there is also evidence of axis cylinder disintegration, the fibres being swollen, ballooned, and granular (Figs. 7 and 8). Not all the fibres are affected in any one tract and, as in the peripheral nerves, they do not begin to degenerate at the same time. The fact that the greatest amount of degeneration in the ventral tract occurs caudally and that in the dorso-lateral tracts occurs rostrally indicates that the same peripheral progression of the change is taking place in these tracts as has been noted in the peripheral nerves, and in the same manner it indicates that the changes are essentially Wallerian or secondary in character. The morphological changes in the axon and the fact that disintegration of the latter is in sufficient abundance to account

FIG. 2.—Marchi preparation of the sciatic nerve cut in longitudinal section. The branch to the main muscles of the leg shows many degenerating fibres, while the other, which passes to the lower leg, is scarcely affected in this case. Seventeenth day. Swank-Davenport. × 55.

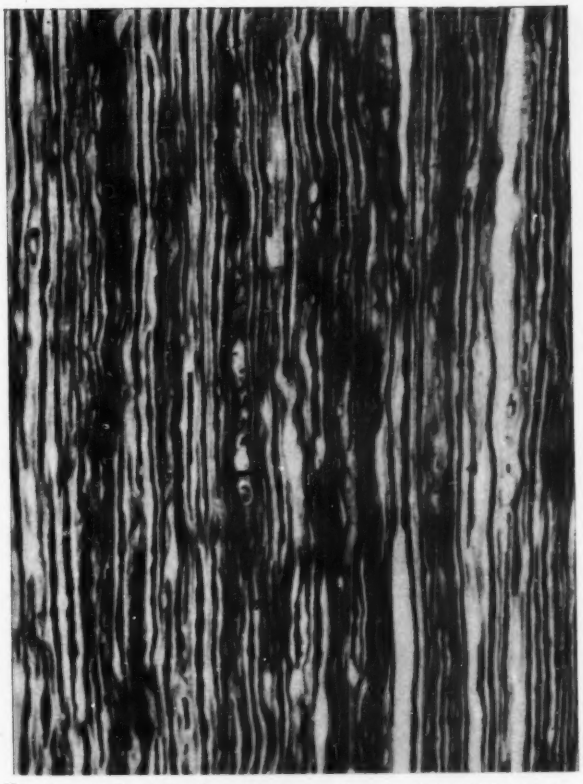

FIG. 3.—Sciatic nerve from the proximal part of the thigh showing only a very low fragmenting fibres. Glees and Marsland silver stain. × 239.

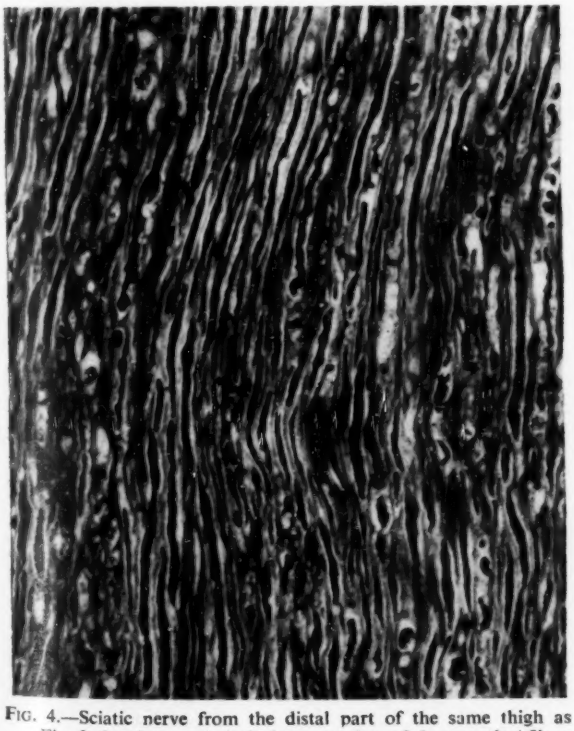

FIG. 4.—Sciatic nerve from the distal part of the same thigh as Fig. 2 showing a relatively large number of degenerating fibres in different stages of disintegration. Glees and Marsland silver stain. × 239.

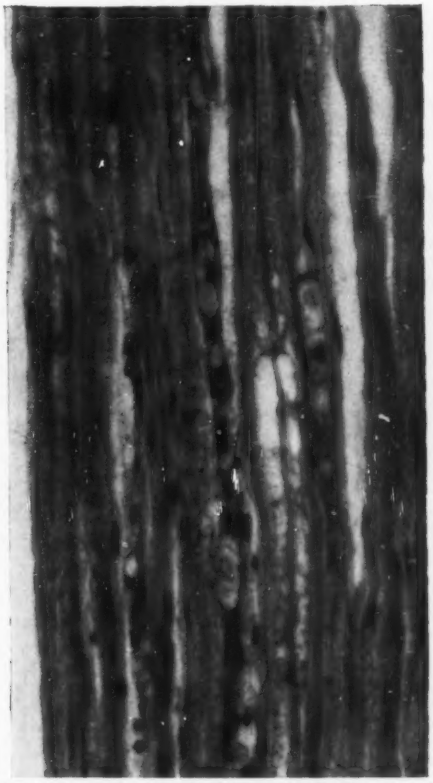

FIG. 5.—Sciatic nerve showing three degenerating fibres with Schwann cell and macrophage proliferation in different stages of progression. Haematoxylin and eosin. × 350.

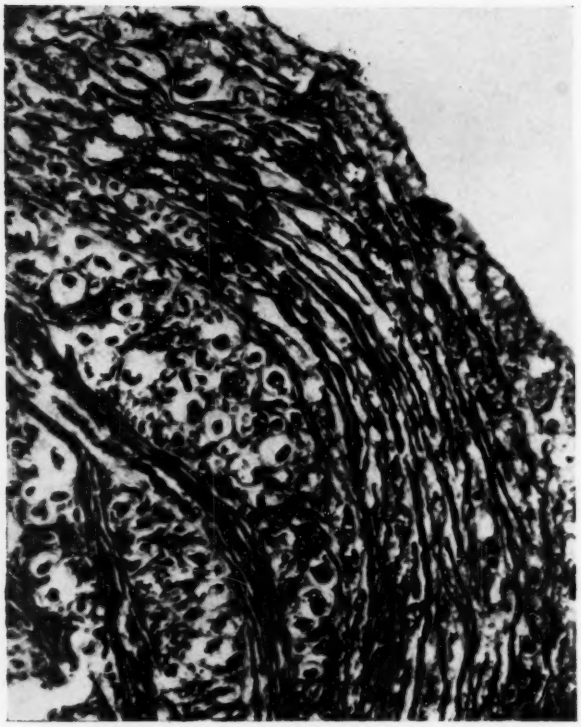

FIG. 6.—Transverse section of medulla 13 days after poisoning, showing fragmentation of a few fibres in the dorsal cochlear commissure. A few ballooned and fragmenting fibres are also visible in the medial longitudinal fasciculus cut transversely. Glees and Marsland silver stain. × 285.

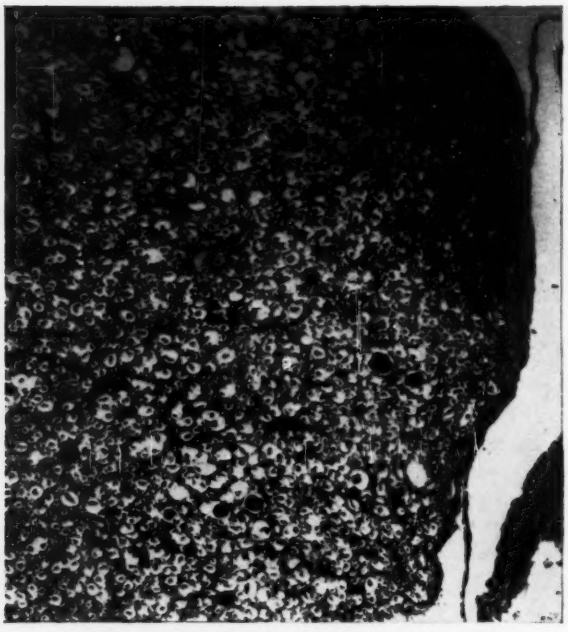

FIG. 7.—Swollen axis cylinders in the spino-cerebellar tract seen in transverse section in the upper cervical region 20 days after poisoning. Same stain as Fig. 5. × 105.

satisfactorily for the changes in the myelin sheath give support to this concept.

Despite a systematic search for an initiating lesion in the different regions of the spinal cord, it was not possible to discern any changes in the nervous tissue before there were definite symptoms of damage; it is apparent, therefore, that these nervous symptoms are the result of the degeneration in the main fibre tracts and are probably not due to any other mechanism.

FIG. 8.—Swollen and granular fragmenting axis cylinder seen in longitudinal section in the ventral tract of the thoracic cord 13 days after poisoning. Same stain as Fig. 5. × 465.

The Nerve Cells.—Since it is evident that axonal degeneration occurs both in the central tracts and in the peripheral nerves it might be expected that changes either of a primary or of a secondary nature might be present in the nerve cells of the affected fibres. Examination of the spinal cords up to the thirty-fifth day after dosing with T.O.C.P. shows, however, that there are no changes in the nerve cells that could be held to account for the extensive damage to the nerve fibres, and this is in accordance with the observations of other workers. Except for the presence of one chromatolytic cell in the dorso-medial column in the lumbar region in one case at

the twenty-eighth day, there was also no evidence of secondary chromatolysis, a finding which is surprising in view of the extensive damage that was frequently met with in the sciatic nerve. The possibility that T.O.C.P. in some way interfered with this reaction was excluded by experiment, when it was found that an approximately similar degree of chromatolytic change could be produced by surgical section of the sciatic nerve in the presence of T.O.C.P. intoxication as in control birds.

Preparations by the DaFano method to show the Golgi apparatus did not reveal any deviation from the normal during the first three weeks after poisoning. Not infrequently lipoid granules made visible by the chlorate-osmic acid technique were seen in the cytoplasm of the nerve cells. Similar granules were noted by Smith and Lillie (1931); their significance is not clear. No changes of note were discerned in any other cells of the spinal cord or of the brain-stem or cerebellum.

The Glial Cells of the Fibre Tracts.—No alterations in the appearance or the numbers of the glial cells of the spinal cord or of the brain-stem are discernible during the first two weeks after the administration of T.O.C.P. Thereafter there is a slight numerical increase in microglia, and astroglia also begin to multiply in the degenerating tracts, becoming moderately numerous by the fourth week. During the crucial first eight to 10 days before the onset of severe symptoms no changes can be observed in the oligodendroglial cells.

A Note on Some Features of the Anatomy of the Important Tracts of the Spinal Cord of the Chicken

The anatomical arrangement of the spinal tracts of birds is unlike that of other vertebrates in several important respects. The most significant difference is the absence of a cortico-spinal tract, the cerebral cortex of birds being small and having connexions only with the diencephalic and midbrain regions (Huber and Crosby, 1929). The place of the pyramidal tract of other species appears to be taken by the large-fibred ventral tract that runs the whole length of the cord and can be traced rostrally into the ventral aspect of the median longitudinal fasciculus on either side of the median raphe. Cordotomy studies performed in the upper thoracic region show this tract to be essentially descending and its fibres pass into the anterior horns (Fig. 10). Its origins, however, are less clear and little mention of them can be found in either Ramon Cajal's (1911) or in Ariëns Kappers, Huber, and Crosby's (1936) volumes on the comparative anatomy of the nervous system. Papez (1929), with whom Swank and Prados (1942) agree, states that this tract arises from the optic tectal region which is very highly developed in birds. Unfortunately no direct reference to original work on this subject is given by Papez, and Boyce and Warrington (1899) and Münzer and Wiener (1898), who carried out ablations of the optic lobes in birds, do not describe degenerative changes in the ventral tract following this procedure. Münzer and Wiener do, however, show with the Marchi technique two small tracts in the lateral columns which they consider spring from nuclear masses in the depths of the optic lobes. These latter tracts are relatively insignificant in comparison with the ventral, both in size and in the degree of myelination, and moreover they do not appear to extend the whole length of the cord. Interruption of the ventral tracts leads to ipsilateral spastic paresis with increased reflexes, so that

FIG. 9.—Lumbar cord 24 days after poisoning, showing degeneration in the ventral tract. Swank-Davenport. × 18.

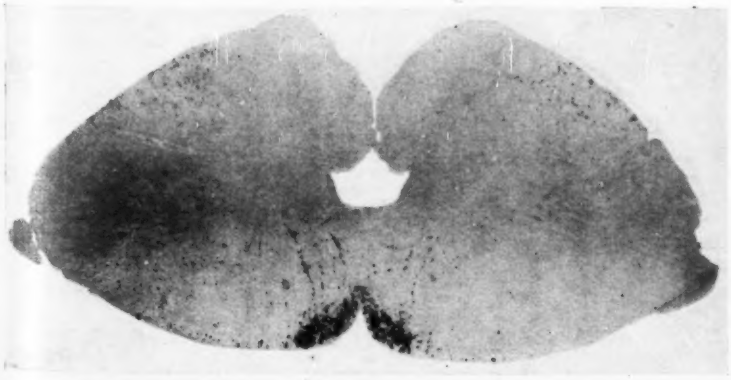

FIG. 10.—Lumbar cord 14 days after upper thoracic cordotomy, showing the degenerating descending fibres in the ventral tract and passing into the anterior horn. The tract is identical in position with that shown in Fig. 9. Swank-Davenport. × 14.

functionally they would seem to resemble the pyramidal tract of other species. Although ablation experiments in the author's hands have not yielded any further information than that already noted above, it is felt that on the available evidence the cells of origin of this tract would be more likely to be found in relation to the midbrain, which is the dominant reflex-controlling centre, than in any other part of the brain-stem. Despite this lack of precise knowledge it is sufficient for the problem in hand to recognize that the fibres of the ventral tract are essentially motor and of much functional importance, and further that the course they run is one of the longest of any in the nervous system of the bird.

The spino-cerebellar tracts of birds, as might be expected from the refined sense of balance of this species, are conspicuous and contain a high proportion of heavily myelinated fibres. The investigations of Friedländer (1898) and of Ingvar (1918) have shown that they arise from the thoraco-lumbar regions and that they contain both crossed and uncrossed fibres. The great majority of these, probably all (Whitlock, 1952), terminate in the cerebellar cortex, distributed chiefly to the anterior folia, while a few scattered fibres pass to the pyramis and uvula of the posterior folia (Whitlock, 1952).

In contrast to the spino-cerebellar tracts the long fibres of the posterior columns of birds are poorly represented and are found in a narrow column on either side of the midline. The great majority of the fibres lying between the posterior horns of grey matter are short inter-calatory fibres linking adjacent levels of the cord and are thus of reflex importance only (Streeter, 1904).

Discussion

Because of its ready susceptibility the domestic hen has been previously used in the study of T.O.C.P. intoxication of the nervous system by Smith and Lillie (1931) and by Sampson (1942), while more recently Barnes and Denz (1953) have shown a similar susceptibility to the other organo-phosphorus compounds di-*iso*-propylfluorophosphonate (D.F.P.) and "mipafox", both of which produce changes in all essentials identical with those of T.O.C.P. With all three compounds the last authors have shown that by using repeated doses other laboratory animals can be paralysed but with considerably less ease and regularity than can the hen. Man appears to resemble the hen with regard to susceptibility both to T.O.C.P. and to the other organo-phosphorus compounds mentioned, and pathologically the changes are essentially the same in both subjects. It appears, however, that after ingestion of T.O.C.P. there occurs in man a greater amount of recognizable nerve cell damage (Bowden, Turley, and Shoemaker, 1930; Goodale and Humphreys, 1931; Vonderahe, 1931) than is found in the spinal cord of the hen, chromatolytic change in particular being a feature in the anterior horn cells. Studying the later stages of the condition Aring (1942) found in man degeneration of the pyramidal tracts, the spino-cerebellar tracts, and also of the tract of Goll but not of that of Burdach. In peripheral nerves in all species in which paralysis can be accomplished the sciatic nerves are always more severely and extensively damaged than any other, though nerves to the upper limb may be also affected but to a lesser degree. Not all fibres are attacked in any nerve and mostly only a small proportion show degeneration, but it is evident that the fibres of large diameter and of greatest length are especially chosen, with the result that the distal extremity is more seriously affected and the functional disturbance is predominantly motor rather than sensory. Moreover, a greater degree of degenerative change is visible in the distal part of the nerve than occurs in the proximal part.

In the spinal cord the species differences that are found in the various tracts affected are significant only in that they underline the fact that it is the functionally important tracts containing a high proportion of heavily myelinated fibres of considerable length that suffer damage. It is significant, for instance, that Goll's tract in man is more affected than Burdach's and that the posterior columns are more susceptible in mammals than they are in the bird. These columns in birds have only a fraction of the importance and consequently of the size that they possess in mammals, and it is to be expected that the spino-cerebellar tracts rather than these should bear the brunt of the effects of the poison in birds while in mammals there is a more equal distribution of changes between the two. Of the descending systems, the pyramidal tract in man and other mammals is almost exclusively involved while in birds its homologue the ventral tract is similarly attacked, and it must be apparent that as in the case of the peripheral nerves the functional activity of the fibres is of importance in predisposing them to the toxic action of T.O.C.P.

Since the early investigations of T.O.C.P. intoxication the view has become current that the process in the nervous system is one of primary degeneration of the myelin sheaths, a view based very largely upon the almost exclusive use of the Marchi technique or its modifications. It is clear from the present findings, however, that axis cylinders are destroyed equally with their sheaths and the sequence

of events closely follows that of Wallerian degeneration. Though a careful search was made no evidence could be found for believing that disintegration of myelin was preceding axis cylinder fragmentation by any significant length of time; in dissociated preparations of peripheral nerve it was seen that the myelin changes were similar in all the internodal regions along the length of the individual fibres followed. If the disintegration of myelin was consequent upon some local metabolic inadequacy, which a hypothetical toxic action would imply, then it would be expected that disintegration of the sheath might occur segmentally at least during the early stages of the process, since it is probable that the internodal stretches of sheath are isolated units controlled by the adjacent Schwann cell. Such focal lesions were never observed even in the early stages of the degeneration. Moreover, it is doubtful if myelin degeneration *per se* can produce such a rapid and uniform effect upon its enclosed axon as was observed here, and three dissimilar lines of evidence tend to support this view. The first is the frequent persistence of axons in the plaques of disseminated sclerosis even when they have been stripped of their covering myelin, and the second is the observation of Speidel (1933) that segments of myelin may break down during the development of the amphibian nerve without any apparent adverse effect upon the nerve fibre. Further, Swank (1940) has observed that in starvation in rats the myelin may undergo fragmentation while the axon remains intact.

Attention has been paid in this study to this aspect of the relationship between the myelin sheath and its axon because of the suggestion put forward earlier by Earl and Thompson (1952) that the pseudocholinesterase of the Schwann cells and the glia might play some part in the metabolism of myelin and that the demyelinating action of T.O.C.P. could conceivably therefore be the result of inhibition of this enzyme. As knowledge of the anticholinesterase effects of the organo-phosphorus compounds extended, however, it became apparent that this view could not be sustained (Thompson, 1953), because even though they all appeared to have a more or less equal anticholinesterase effect, only a few were capable of damaging nervous tissue. Moreover, Webster (1954) has shown with the aid of radioactive tracer elements that there is no appreciable change in the turnover of lipoid phosphorus in peripheral nerve during the period of depressed pseudocholinesterase activity following the administration of T.O.C.P. and thus no support is given to the thesis that this enzyme is concerned with the synthetical processes of myelin metabolism. Davison (1953) tested five organo-phosphorus compounds for their anticholinesterase effects and found that although they had an almost equal action upon the enzyme only two, namely D.F.P. and "mipafox", were capable of causing demyelination whereas bis (di-*iso*-propylamino) phosphonous anhydride (iso-O.M.P.A.), O.O. di-*iso*-propyl O. p-nitrophenyl phosphate (iso-E600), and tetra-*iso*-propyl pyrophosphate (T.I.P.P.) had no such effect. Similar results were recorded by Barnes and Denz (1953) and the conclusion was drawn that for the production of demyelination mere depression of the pseudocholinesterase is insufficient. In corroboration it may be mentioned that although demyelination has been produced in ruminants by Smith, Elvove, and Frazier (1930), Smith and Lillie (1931) and Draper, James, and Johnson (1952) only a low activity of pseudocholinesterase can be detected in the brains of sheep and oxen (Gunter, 1946; Mendel and Myers, 1952). On the other hand Mendel and Myers (1952) found in the rat that even though the brain pseudocholinesterase can be reduced to zero activity for several weeks with T.O.C.P. there is no apparent effect upon the health of the animals. On the evidence it is difficult to believe that interference with this enzyme is of primary importance to the nutrition of the myelin sheath in such widely different species as birds and man, while in others it is singularly inert in this respect. The facts strongly suggest that attention should be turned away from the Schwann cells and the glia as being of importance in the pathogenesis of the lesions in T.O.C.P. poisoning and towards the possibility of the neuron being primarily affected.

The main argument in favour of interference with the metabolism of the nerve cell as being the primary change produced by T.O.C.P., and probably also by the other organo-phosphorus compounds that have similar effects upon the nervous system, is the close similarity that exists between the changes produced by these substances and those found in chronic thiamine deficiency. This relationship was initially pointed out by Aring, Bean, Roseman, Rosenbaum, and Spies (1941) and has been stressed more recently by Barnes and Denz (1953). On closer examination these similarities are very striking. The particular susceptibility of the avian species and of man is common to both and in both there is a significant period of delay before the appearance of functional and structural disturbances. Moreover, the pattern of the lesions in each condition is the same, not only in the especial involvement of the distal parts of the fibres, but also in the distribution of the tracts concerned. In the bird the spinocerebellar and the ventral tracts are particularly

picked out in both diseases, while the vestibulocochlear system, as observed here for T.O.C.P. and in thiamine deficiency by Swank and Prados (1942), is also damaged. In neither condition is the perikaryon noticeably affected except in the later stages when cell shrinkage or chromatolysis may be observed. The biochemical mechanism of the changes in thiamine deficiency is now generally accepted as resulting from the slowing of the energy-producing pyruvate oxidation cycle which leads to degeneration of those parts of the nerve cell farthest from the cell body (Swank and Prados, 1942). In T.O.C.P. poisoning Earl, Thompson, and Webster (1953) found that this cycle was unaffected in this condition, but since only brain was studied and not other parts of the nervous system, the possibility that the respiration mechanism is disturbed cannot be completely excluded. The similarities between the two conditions are so close as to suggest very strongly that there may be a common final pathway through which the ultimate changes are brought about.

One further aspect of the problem deserves mention since it has not been fully investigated to date. Both T.O.C.P. and the organo-phosphorus compounds affect aliesterases to a variable degree, though information about this and other aspects of these enzymes is not so precise as it is with the cholinesterase. With T.O.C.P. Earl and his colleagues (1953) found a partial inhibition of tributyrinase to about 50% of its original activity in chicken brain. It would be of interest to know more about this aspect of the question since it is possible to demonstrate distinct differences in the amount of aliesterase in nerve cells. For instance, using the α-naphthol acetate method of Gomori (1952), which presumably visualizes the activity of esterases of the type with which we are concerned, a large amount of enzyme activity can be shown to be present in the anterior horn cells of the spinal cord of the rat and the guinea-pig, while there is practically none in the same cells in the chicken. It would seem reasonable to suggest that even a partial inhibition of enzyme of initially low activity might be sufficient to render it inadequate for efficient cell metabolism. Moreover, variations in the amount of enzyme and its sensitivity might well contribute to the marked differences in the response of the various species to poisoning with these substances. Since the function of the aliesterases in nature is as obscure as that of pseudocholinesterase, the possibility that they may be concerned in the production of the changes in the nervous system due to T.O.C.P. cannot be considered to be completely unworthy of further examination.

Summary

The changes in the nervous system following poisoning with T.O.C.P. have been studied, and degeneration of axis cylinders and myelin sheaths in both the peripheral nerves and long tracts of the spinal cord is found. The degeneration appears to affect the distal extremities of the axons, and long fibres of large diameter are particularly selected.

The closeness with which these changes resemble those of thiamine deficiency is stressed and it is suggested that there may be a mechanism producing neuronal damage common to both conditions.

The relation between damage to nervous tissue and the inhibition of pseudocholinesterase by T.O.C.P. is examined, and it is concluded that this is probably not of primary significance.

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References

Ariëns Kappers, C. U., Huber, G. C., and Crosby, E. C. (1936). *The Comparative Anatomy of the Nervous System of Vertebrates including Man*, 2 vols. Macmillan, New York.
Aring, C. D. (1942). *Brain*, **65**, 34.
——, Bean, W. B., Roseman, E., Rosenbaum, M., and Spies, T. D. (1941). *Arch. Neurol. Psychiat., Chicago*, **45**, 772.
Barnes, J. M., and Denz, F. A. (1953). *J. Path. Bact.*, **65**, 597.
Bloch, H. (1941). *Helv. med. Acta*, **8**, Suppl. 7, 15.
Bowden, D. T., Turley, L. A., and Shoemaker, H. A. (1930). *Amer. J. publ. Hlth*, **20**, 1179.
Boyce, R., and Warrington, W. B. (1899). *Proc. roy. Soc.*, **64**, 176.
Burgen, A. S. V., and Chipman, L. M. (1951). *J. Physiol.*, **114**, 296.
Davison, A. N. (1953). *Brit. J. Pharmacol.*, **8**, 212.
Draper, H. H., James, M. F., and Johnson, B. C. (1952). *Fed. Proc.*, **11**, 204.
Earl, C. J., and Thompson, R. H. S. (1952). *Brit. J. Pharmacol.*, 7, 685.
——, ——, and Webster, G. R. (1953). *Ibid.*, **8**, 110.
Friedländer, A. (1898). *Neurol. Zbl.*, **17**, 351 and 397.
Glees, P., and Marsland, T. A. (1952). *J. Physiol.*, **118**, 51*P*.
Gomori, G. (1952). *Int. Rev. Cytol.*, **1**, 323.
Goodale, R. H., and Humphreys, M. B. (1931). *J. Amer. med. Ass.*, **96**, 14.
Gunter, J. M. (1946). *Nature, Lond.*, **157**, 369.
Hottinger, A., and Bloch, H. (1943). *Helv. chim. Acta*, **26**, 142.
Huber, G. C., and Crosby, E. C. (1929). *J. comp. Neurol.*, **48**, 1.
Hunter, D., Perry, K. M. A., and Evans, R. B. (1944). *Brit. J. industr. Med.*, **1**, 227.
Ingvar, S. (1918). *Folia neuro-biol. Lpz.*, **11**, 205.
Koelle, G. B. (1950). *J. Pharmacol.*, **100**, 158.
Mendel, B., and Rudney, H. (1944). *Science*, **100**, 499.
——, and Myers, D. K. (1952). *Nature, Lond.*, **170**, 928.
Münzer, E., and Wiener, H. (1898). *Mschr. Psychiat. Neurol.*, 3, 379.
Ord, M. G., and Thompson, R. H. S. (1952). *Biochem. J.*, **51**, 245.
Papez, J. W. (1929). *Comparative Neurology*. Crowell, New York.
Ramón y Cajal, S. (1911). *Histologie du système nerveux de l'homme et des vertébrés*. Maloine, Paris.
Sampson, B. F. (1938). *Bull. Off. int. Hyg. publ.*, **30**, 2601.
—— (1942). *S. Afr. med. J.*, **16**, 1.
Smith, M. I., Elvove, E., and Frazier, W. H. (1930). *Publ. Hlth Rep. Wash.*, **45**, 2509.
——, and Lillie, R. D. (1931). *Arch. Neurol. Psychiat., Chicago*. **26**, 976.
Speidel, C. C. (1933). *Amer. J. Anat.*, **52**, 1.
Staehelin, R. (1942). *Schweiz. med. Wschr.*, **72**, 1.
Streeter, G. L. (1904). *Amer. J. Anat.*, **3**, 1.
Swank, R. L. (1940). *J. exp. Med.*, **71**, 683.
——, and Prados, M. (1942). *Arch. Neurol. Psychiat., Chicago*, 47, 97
Ter Braak, J. W. G. (1931). *Ned. T. Geneesk.*, **75**, 2329.
Thompson, R. H. S. (1953). *Brit. med. Bull.*, **9**, 138.
Vonderahe, A. R. (1931). *Arch. Neurol. Psychiat., Chicago*, **25**, 29.
Webster, G. R. (1954). *Biochem. J.*, In the press.
Whitlock, D. G. (1952). *J. comp. Neurol.*, **97**, 567.

J. Neurol. Neurosurg. Psychiat., 1954, **17**, 173.

MENTAL DISTURBANCES IN TUBERCULOUS MENINGITIS*

BY

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Ever since tuberculous meningitis was first defined as a specific disease (Whytt, 1768) it has been recognized that disturbances of the mind form an integral part of the clinical picture. As the disease progresses, so these disturbances increase until the illness closes in coma and death. Thus the classical descriptions of the disease insist on apathy, irritability, and insidious changes in personality as among the chief characteristics of the early stages of the illness. Whytt himself, writing of children, says : " Their spirits being low they incline mostly to lie in bed, although they are more often disposed to watching than sleep ". Trousseau (1868) says : " Sadness setting in unaccountably is a premonitory sign of great value in a child " ; while Osler (1892) states specifically that " the personality may completely change ".

Towards the end of the prodromal phase the mental changes deepen to semi-stupor or frank delirium, usually described as either hysterical (Gowers, 1893) or as delirium tremens (Barlow, 1899). The prominence of the mental symptoms is reflected in the discussions of the differential diagnosis. Two conditions often confused with tuberculous meningitis were hysteria and typhoid fever. Both typhoid fever and tuberculous meningitis are characterized by headache, fever, and delirium, and the likeness between the two is still acknowledged by the use of the term " the typhoid state " in modern accounts of general tuberculosis (Gow and Bodley Scott, 1950).

In doubtful cases the point at issue was whether the delirium should be ascribed simply to general toxaemia or to direct cerebral insult. Wilson (1844), writing of acute rheumatic fever, had urged that " it be remembered in the treatment of ' head symptoms ' incidental to this as to other forms of acute disease, that the brain may be unsettled by many influences that do not originate within the brain itself ".

Gowers (1893) recognized both general and local causes for mental disturbances but suggested that they could be distinguished clinically. When discussing the differential diagnosis between tuberculous meningitis and typhoid fever, he says :

" The error always arises from ascribing initial headache and subsequent delirium to cerebral disease in the presence of sufficient pyrexia to account for the symptoms and from disregarding the relation between the two. When they are the result of general disease, as Sir William Jenner long ago pointed out, the headache ceases when the delirium begins."

Today there is good reason to believe that the mental disturbances of tuberculous meningitis are the direct result of the infection of the brain. But the problem of whether these disturbances differ in kind from those encountered in other organic confusional states has not been resolved ; still less the question of whether these mental changes can be attributed to injury of any particular part of the brain.

Organic confusional states are commonly classified as the acute—which are characterized by delirium, disorientation, hallucinations and, sometimes, coma-vigil—or as chronic—characterized by mental dulling, amnesia, and disorder of the emotions. In the first, recovery is said to be sudden and complete except for amnesia for the actual period of confusion. We have not found any detailed account in the literature of the pattern of recovery in the chronic group, though a few cases are reported in which recovery, or at least improvement, took place (Korsakoff, 1889 ; Jolliffe, Wortis, and Fein, 1941). Tuberculous meningitis is now a treatable disease, and recovery can be expected in over two-thirds of all cases, but not infrequently this takes place after periods of confusion lasting for months. Cases of tuberculous meningitis under treatment therefore provide a new field for the study of organic confusional states since, on the one hand, these cases cannot conveniently be classified as either acute or chronic, while, on the other, they afford ample opportunity for observations on the pattern of recovery.

* This study was begun by one of us (M. W.) in conjunction with the late Sir Hugh Cairns. Since that time additional material has come to hand which has allowed the work to be completed.

The results of such a study are reported here in the hope that they may help to elucidate the pattern of recovery from organic confusional states in general, and may also help to determine the degree of recovery and the nature of the residual disturbance after long periods of semi-consciousness and dementia.

Material and Methods

Our material was drawn from cases of tuberculous meningitis treated at the United Oxford Hospitals and the Military Hospital for Head Injuries, Wheatley. This particular study was largely confined to those adults who, though drowsy and irrational, were yet alert enough to answer questions and permit of some form of psychological assessment.

Whenever possible, the patient's intellectual capacity was assessed by intelligence tests adapted from the Wechsler and Terman-Merrill scales. Memory span was assessed by digit repetition and by repetition of sentences from the Babcock scale. Learning was measured by the Rey-Davis Test; by ability to learn a set of digits or a sentence slightly longer than the immediate memory span; and by learning of the paired-associates from Wechsler's Memory Scale. Delayed recall was measured by the ability to recall pictures or numbers a short time after they had been presented; by reproduction of the Babcock designs from memory test; and by the progressive prompting technique (Williams, 1953).

It will be appreciated that the tests had to be chosen to suit each individual and that few patients were subjected to the full battery.

The Prodromal Phase

We have little to add to existing descriptions of the mental changes in the prodromal phase, though it is worth noting that in one case the presenting symptom was a subjective impairment of memory. Typically, the earliest mental changes are so insidious that they may be imperceptible to one who did not know the patient before his illness. Sometimes, however, when the patient is convalescent it becomes obvious in retrospect that personality changes were in fact present during the active stage of the disease. Thus, a child under treatment may for weeks seem fully conscious and alert, spending his time sitting up in bed playing with his toys, yet he may remain sullen, uncooperative, and withdrawn. In view of his apparent well-being he is probably judged to be spoilt or shy, or his attitude is attributed to a justifiable dislike of doctors. And then, quite suddenly, he becomes friendly and smiling and anxious to be talked to and played with. When such case records are studied in retrospect it is found that this improvement has coincided with some other favourable change, such as a fall in the protein content of the cerebrospinal fluid (C.S.F.), or the beginning of a persistent gain in weight, that is in itself evidence that the meningeal infection is obsolescent.

There is one negative finding of considerable diagnostic value that should be mentioned. These patients, even in the early stages of the disease, lack the over-alert, apprehensive expression so often seen in pre- or non-paralytic poliomyelitis (Russell, 1952). Irritable as they are, when undisturbed they lie on one side with their eyes closed, and the first perceptible mental change is a faint clouding of awareness.

The Fully-developed Disease

In our experience the mental disturbances seen once the full clinical picture of tuberculous meningitis has developed may vary in degree from case to case, but in kind are remarkably constant. The characteristic picture is well shown by the following case.

Case 1.—M. C., aged 19 years, was admitted to hospital on November 16, 1950. The history and physical findings were strongly suggestive of tuberculous meningitis. Treatment with streptomycin was begun within 24 hours and the diagnosis later confirmed by identification of *M. tuberculosis* in the C.S.F.

On admission he was drowsy, confused, disorientated, and incontinent of urine and faeces. The degree of drowsiness fluctuated, but he never became deeply unconscious.

He remained in this state for the first five days, and then, on November 22, he began to improve. He still slept most of the time but woke as soon as he was spoken to and was very cheerful, indeed euphoric. He was now orientated in place and time, could describe pictures accurately, and showed a fair ability on intelligence tests. For example, his performance on the Wechsler similarities was equivalent to an I.Q. of 110. Immediate rote memory and learning were up to average. On Babcock's sentence repetition test he repeated the sixteenth sentence correctly at the first trial, and the twenty-third correctly at the third trial.

In spite of this good performance, he was totally unable to retain memories for any length of time and when pressed would confabulate freely. For example, even after half an hour he had little recollection either of the tests he had done or of the pictures he had been shown. On one occasion he tried hard to remember the examiner's name, but when seen by the same examiner a week later denied ever having seen her before. His memory for the eight months before his illness was also extremely vague. He could name the camps he had been

in, but could not say for how long, or in what order, he had been in each. He talked a great deal about his girl-friend, but had no idea where they had first met. He also had several vivid recollections of football matches, but did not know when he had played them. By contrast, his memory for events preceding his entering the Army, three months before the onset of his illness, seemed to be intact : he gave a good account of his childhood and the work he had done before he was called up.

During the next five to six weeks he showed sustained improvement in spontaneous activity and intellectual ability, and grew less euphoric. But although his retrograde amnesia steadily shortened, improvement in memorizing was very slow. Thus, although about this time he became able to remember the names of his doctors, he could not remember the contexts of their visits. He read many books each week, but shortly after they had been removed from his bedside he was unable to give their titles or recount any of their contents. Formal test material was also poorly retained. His performance on the Wechsler Similarities Test was equivalent to an I.Q. of 120 (i.e., it showed a gain of 10 points), but his answers to some of the questions on the Wechsler Comprehension Test were poor and lacking in insight. (For example, to the question, " Why should we keep away from bad company ? " he answered, " You don't want to get into it ".)

By January 5, 1951, two months after the onset of his illness, his behaviour was quiet and responsible. The defect of memorizing had recovered, and he had no longer any difficulty in retaining the names of his attendants or the test material. He was no longer incontinent. The Wechsler Comprehension Test indicated some slight further improvement in thought processes. The retrograde amnesia had largely disappeared, though his memory for events of the week immediately preceding the onset of his illness was still very hazy.

At this stage the onset of deafness due to the streptomycin made conversation difficult, but it was apparent from those tests that could be applied that intellectual ability and memorizing were well up to average. He reproduced the " Designs " from the Stanford-Binet test, Form I, correctly two weeks after seeing them at a single presentation. On the Rorschach test he gave many well-integrated responses indicating a high level of intelligence. By contrast with this excellent recovery of his intellectual faculties he still had a complete amnesia for the first six weeks of his illness and a retrograde amnesia for one week preceding its onset.

When he was discharged from hospital in July, 1951, his parents considered that his previous ability, personality and interests were fully restored ; and subsequent follow-up studies confirmed that physical and mental recovery were complete except for the deafness and the amnesia for the first weeks of his illness.

In this and similar cases analysis of the illness, according to the defects exhibited at different times, allows three successive mental states to be distinguished. We have called these the confusional state, the amnesic state, and the post-recovery state.

The Confusional State.—During the early days of the illness patients are apathetic and lack initiative. Although when roused they may appear fairly alert, they are grossly disorientated in space and time. There is great poverty of speech, and they are quite incapable of sustaining any rational conversation. Thus in many respects the picture resembles that described in other acute organic confusional states (see e.g., Henderson and Gillespie, 1936).

The Amnesic State.—This more or less coincides in time with the period during which patients remain critically ill : it corresponds in fact with what has been called " the period of deadlock " (Cairns and Smith, 1952 ; Smith, 1953). Though patients may be sufficiently alert and rational to occupy themselves and to cope adequately (though not yet quite normally) with intellectual problems, they have the greatest difficulty in retaining any new impression for more than a few minutes. Memory for remote personal events is commonly intact, but for the events of the illness and for those that have preceded it by anything up to several months it is hazy and poorly integrated. Euphoria or depression and total lack of insight are the rule, as is incontinence of urine and faeces. Patients thus exhibit all the major symptoms of the chronic organic confusional state.

The Post-recovery State.—Once the amnesic state has passed mental recovery, as assessed from the observations of relatives, from performance at work, and from psychological tests, is sustained and complete except for the residual amnesia.

Nineteen adult patients, all of whom had been confused and amnesic, were examined at various intervals up to four years after the onset of the illness in an attempt to assess the frequency and nature of any residual mental disability. Such a disability can only be assessed in relation to the patient's original personality and abilities. In point of fact, many of our patients had very humble backgrounds, and, as a whole, their scholastic standards were low. Thus not only were three of our adult patients virtually illiterate, but from a total of 31 Service men there was only one officer, while among the adolescents there was only one public-school boy. In this respect these patients differed markedly from those composing a series of 50 unselected cases of pneumococcal meningitis treated at Oxford.

The findings in these 19 cases are summarized in

TABLE I

RESIDUAL MENTAL DISTURBANCE IN 19 ADULT PATIENTS CONFUSED DURING THE ILLNESS

Nature of Disturbance	Present	Absent
Defects of intellect	0	19
Defects of memorizing	4*	15
Defects of personality	3*	16
Amnesia for time of illness	19	0
Retrograde amnesia	6	13

* Subjective disability not confirmed by objective tests.

Table I. No measurable disturbance of intellect, personality, or memorizing was found in any case; and although four patients complained of forgetfulness for minor day-to-day events, this was not confirmed by the memory and learning tests. Three other patients complained of, or were said by their relatives to show, slight defects in concentration and sense of responsibility. There was, however, in each some indication that the past illness was being used as an excuse to cover a fundamental difficulty in personality or social situation.

The residual amnesia was in marked contrast to these trivial changes. None of the 19 patients had any recollection of the first few weeks or months of the illness, and six had in addition a considerable retrograde amnesia. In four cases this retrograde amnesia extended backward for more than a year—in one case for at least four years—before the onset of the illness. As a whole this retrograde amnesia was seldom uniform or global but consisted rather of an inability to organize past events in correct temporal sequence, of memory gaps, and of haziness of memory, as in the following case.

Case 2.—E. C. (Cairns and Taylor, 1949; Case 4), aged 22, developed tuberculous meningitis early in March, 1947. His scholastic career was exceptional in this series. He had matriculated at 15, had passed top of a book-keeping class at night school, and again passed out first from the clerical course he took while serving in Germany. Early in 1946 he had been posted to Germany, and in September, 1946, six months before the onset of his illness, he had taken a clerk's course and had received a fresh posting to a regiment stationed in the Ruhr.

He had a long and difficult illness, with a typical amnesic state and period of deadlock lasting in all about four months, and complicated by severe hypertension of central origin. He was discharged cured at the end of January, 1948.

He was seen in December, 1950, almost four years after the onset of his illness. He was then extremely well; he was working full-time as a clerk, had been promoted and had recently become engaged to be married. On questioning it was found that his amnesia for the first four months of his illness was still complete. Moreover, he was aware of profound defects in his memory for the whole of the time he had spent in Germany. He said: "For this period I have no consecutive stream of memory. When I try to think back, I am very hazy. Some events stand out but I can't chronicle them with clarity. One incident I remember very clearly. I can place it about the spring of 1946 because of world events which I remember were going on at that time."

For the six months spent in Germany which immediately preceded his illness his loss of memory was virtually complete. During that time he had learnt typewriting and had apparently become quite proficient; but on recovery he had no recollection of the course except for a large sheet of letters hanging on the wall, of which the first were Q W E R T. Recently he had been sent a photograph of the men on his course. He found he could name them all without difficulty, although he had no idea whatever of when or where he had met them.

After the course he appears to have gone to Berlin, where he has an undated recollection of visiting the Berlin Zoo and of his horror at the emaciation of the animals.

For his life before he went to Germany and after recovery from the active phase of his illness his memory was intact.

He was last seen in February, 1953, when he was still in the best of health and the amnesia was unchanged.

This patient was sufficiently intelligent to give an excellent account of his amnesia and also to allow an accurate comparison to be made between his mental capabilities before and after his illness. He provides an excellent example of the compatibility of a profound and extensive retrograde amnesia with full intellectual recovery.

Variations from the Typical Picture

Variations from this typical picture have been seen at all its stages and are most commonly those of degree. The acute confusional period may be absent, or intensified to the point where the patient is hallucinated and so wildly delirious that he is almost or completely inaccessible from the outside world. In two relapsing cases the patients at the onset of the relapse were not only hallucinated but terror-stricken, a condition reminiscent of the "delirium tremens" well described by the older authors (Barlow, 1899).

During the amnesic period some patients, instead of being euphoric, were withdrawn and negativistic, or even acutely depressed. Thus certain patients would refuse to eat and when compelled to do so would keep mouthfuls of food tucked into their cheeks for hours at a time. In two cases this refusal to eat persisted as a kind of anorexia nervosa well into convalescence: one patient who had to be fed by means of a constant intragastric milk drip would lean out of bed and turn off the drip whenever the nurses were not watching him.

The greatest variation in the amnesic period was

in its duration. Although in some successful cases it lasted for only two or three weeks, in others it was prolonged for months, and some patients were still unable to retain recent impressions long after their physical recovery was assured.

In fatal cases in which death was due to uncontrolled meningitis the mental confusion persisted and increased in intensity until stupor and coma supervened. In three fatal cases, and three only, the patients seemed to remain fully conscious until shortly before death. Two of these patients were small children and detailed studies were therefore impossible. The third was a girl of 14 years who was undoubtedly lucid for weeks in spite of her uncontrolled infection. These cases will be referred to again.

As might be expected, the permanent loss of memory for the illness itself, like the retrograde amnesia (Table II), tended to vary in extent with the duration of the period of confusion, but was often longer than the course of the illness suggested. Thus, although residual mental disturbances were not anticipated, and accordingly were not systematically sought, in those who had remained lucid throughout their illness a surprising number were found after recovery to be quite unable to recall the early days of their treatment. Although they had always appeared alert, rational, and well able to keep track of their experiences, their impression on looking back was that they must have been unconscious for several weeks.

TABLE II

RELATIONSHIP BETWEEN RETROGRADE AMNESIA AND LENGTH OF CONFUSIONAL PERIOD

Confusional Period	No. of Patients	Duration of Retrograde Amnesia	
		Under One Week	Over One Week
None	14	—	—
Under 1 week	7	2	—
Over 1 week	13	2	7
Total	34	4	7

The Pattern of Recovery

By dividing the mental disturbances seen during the illness into three states, it is not implied that the changes between them were abrupt and measurable. On the contrary, in every case the transition was gradual. For example, the passing of the confusional stage might first show itself by the patient's becoming able to feed himself and then, a day or two later, by his asking for a cigarette or looking at the comic strips in the newspaper. Similarly with the offset of the amnesic stage : a patient who for weeks has denied ever having seen his doctor before will begin to realize that his memory is faulty and say in response to questioning, " I should know your name. I've seen you often enough ". And, a little later, " Oh dear, I've forgotten. And they told me just before you came. It's not X, is it ? " (giving the name correctly). Similarly the patient in Case 4, while still disorientated, would attempt to reconcile his belief that he was still at home with his perception of the hospital environment : " They can make a hospital out of your home nowadays ". The same sequence is shown in regaining sphincter control. The patient is at first incontinent of urine and faeces ; later he regains control over his bowel ; later still he is only incontinent of urine during the night ; and finally he is horrified to be told that he ever wet his bed. The transition from one stage to another is well exemplified by the following case :—

Case 3.—E. G., aged 19, had suffered from idiopathic epilepsy from childhood and was admitted to hospital from an epileptic colony. For the first week in hospital he remained drowsy, confused, and unable to feed himself. During the second week the acute confusional state lightened. He began to sit up in bed and gradually learnt to feed himself until by the end of 12 days he was alert, friendly, and cooperative, but with a gross amnesia for all recent events. Thus he never could remember having seen the ward sister before in spite of the devoted care she gave him. When the trolley was brought for his daily lumbar puncture he would obediently roll over on his side, but as soon as the needle was withdrawn he would deny that he had ever had anything done to his back. He was fully awake all day and occupied himself with handwork or reading the comic strips in the papers, but the moment he was distracted from his occupation he would have no recollection of what he had been doing at the moment of distraction. Many attempts were made to teach him to weave. He would copy the instructor's demonstration correctly, but as soon as his attention was withdrawn from the loom he would deny that he had ever been shown what to do. On several occasions he played a fully competent game of noughts and crosses with the examiner, but when a few minutes later he was shown the sheet of paper on which the game had been played he denied that he had ever seen it before. He maintained that the possessions and letters on his bedside locker belonged to other people.

His orientation in place and time were equally bad. Thus, although he knew that he was not in the Colony, he always maintained that he was somewhere near it. For four months there was little change. He then slowly began to show signs of improvement in memorizing and in orientation. Although on formal testing he would still deny any recognition of test material, he would correctly " guess " what pictures he had been shown a few minutes before. If interrupted in the middle of a task, he would be able to remember what he had been doing, and go on with it. He admitted that the possessions on the locker were his, although unable to describe them

from memory. He realized that he was in a hospital at some distance from his Colony.

Five months after the onset of the illness great improvement was noted. He could repeat a short story correctly and describe pictures several days after they were presented to him. He had great difficulty, however, in learning by rote and was unable to master the Rey-Davis board at the first position, even after five trials. Shortly after this the frequency of his fits increased, and his memorizing ability consequently became difficult to assess.

Although this patient's fits were reasonably well controlled throughout most of his illness, it is possible that the unusual depth and duration of the amnesia was related to the epileptic tendency and that this allowed the recovery phase to be studied, as it were, in slow motion. We have seen a similar delay in mental recovery in elderly patients.

The Specificity of the Mental Changes for Tuberculous Meningitis

The question arises of whether the mental changes described here are specific for the tuberculous intracranial infection or whether they are simply the expression of general toxaemia. There can be no reasonable doubt that they are directly related to the meningeal infection. In the first place, they are not exhibited by patients dying of other forms of tuberculosis, nor are they seen in miliary tuberculosis until the meninges become involved. Secondly, and conversely, we have had several cases in which there was unequivocal evidence that the miliary tuberculosis had healed but in which the meningitis, and with it the mental changes, persisted. Thirdly, an exact correlation can often be established between the intensity of the mental changes and that of the meningeal inflammation. Quite commonly patients under treatment with streptomycin show a sudden spontaneous increase in the cell count and protein content of the cerebrospinal fluid, accompanied by a temporary worsening in their mental and physical state. These phenomena probably represent spontaneous intrathecal tuberculin reactions. Certainly they can be reproduced at will by injecting small amounts of tuberculin directly into the cerebrospinal fluid (Smith and Vollum, 1950).

There is good evidence that these injections are of therapeutic value (Smith, 1953), and it is now our practice when treating tuberculous meningitis to supplement the daily systemic and intrathecal chemotherapy with intrathecal injections of tuberculin. The tuberculin is given about once every four to eight days, and in sufficient amounts to provoke a reaction. This reaction consists of an acute exacerbation of all the signs and symptoms of the meningitis, mental as well as physical. Physically, the patient is feverish, vomits, and complains of headache. The neck stiffness increases or returns, the intracranial pressure rises, and focal neurological signs become more obvious. Mentally, the patient tends during the reaction to fall back temporarily to the level from which he has just recovered. Thus, one who has recently been stuporous and is still very confused will relapse into stupor ; while one who has recovered from his confusion but is still amnesic will again become confused. The following is a typical case :—

Case 4.—J. M., an Irish labourer of 21, was admitted to hospital on June 1, 1950. On admission he was drowsy, confused, and disorientated, and totally uninterested in his surroundings. Focal neurological signs were limited to nystagmus and mild ataxia. Unless disturbed he lay curled up on his side with his eyes closed, and though he could be roused sufficiently to take part in a limited neurological examination it was impossible to hold his attention for more than a few minutes before he would sigh, turn over, and go to sleep again. He was incontinent of urine and faeces. Treatment was begun immediately with intrathecal and intramuscular streptomycin, supplemented by intrathecal injections of tuberculin given about once every four days.

For the next 12 days the patient remained drowsy but could usually be roused to take part in a limited conversation. But for the day after each tuberculin injection he was almost unrousable, and speech, if present at all, was restricted to a few monosyllables.

During the next six weeks he became progressively easier to rouse during the intervals between the tuberculin reactions, and soon was alert enough to cooperate in a fairly extensive psychological examination. This showed him to be grossly disorientated in place and time, and inconsistent in his accounts of himself and his past. He was almost completely amnesic for all day-to-day and moment-to-moment events. For example, on several occasions attempts were made to teach him a simple wire puzzle. Although he struggled to solve it, he could never do so except immediately after each demonstration. He was also frequently shown a series of inkblots which changed from a black circle into the silhouette of a rabbit (Williams, 1953). He never remembered having seen the end of the series when the first was shown to him again. Intellectual ability was very restricted. He gave correct answers to only three questions on the Wechsler Similarities Test, and only five on the Wechsler Picture-Completion Test, a score roughly equivalent to an I.Q. of 55. He treated nurses and staff as old friends, calling them by the Christian names of former acquaintances.

During the 24 hours following each tuberculin injection the patient was much more lethargic, and, though easily roused, was unable to cooperate in any of the above tests.

During the next two weeks the patient's intellectual ability and general attitude showed considerable improvement. For example, by this time he was able to beat

every other patient in the ward at draughts. He would attempt to rationalize the inconsistencies in his orientation, and although he still had difficulty in retaining day-to-day information, he began to show signs of recognizing the pictures that he had seen repeatedly. However, during his tuberculin reactions he would again become as confused and disorientated as ever.

Nine weeks after the onset of his illness he was correctly orientated, could recognize the hospital personnel, and was no longer incontinent. Intellectual ability was greatly improved. He could solve the wire puzzle alone, and his performance on the Wechsler tests indicated an I.Q. of about 97. He took an interest in the affairs of the ward and could give the gist of the daily news. However, during his tuberculin reactions he would again become amnesic and was inclined to be confused. Thus on one occasion he was shown a number of pictures before receiving tuberculin later that evening. The following day he had a typical reaction, and was vomiting and complaining of headache. His orientation remained correct, but he was unable to recall any of the pictures he had been shown the previous evening. Two days later, without any further prompting, these pictures were readily recalled.

To what extent these mental changes are specific for tuberculous meningitis, as opposed to other diseases of the brain, is harder to answer. There is no doubt that their quality is sufficiently constant to be a very considerable help in diagnosis. The lack of anxiety and apprehension in the prodromal phase has already been noted. This is a useful point in the differentiation of tuberculous meningitis from pre- or non-paralytic poliomyelitis. In the latter condition the patient looks ill and flushed and shows a very considerable degree of meningism, but in spite of this he is usually over-alert and obviously apprehensive (*Lancet*, 1953). By contrast, by the time the patient with tuberculous meningitis is showing a comparable degree of meningism and general toxicity, he is, as a rule, already becoming clouded and sleepy.

How useful the characteristic picture of the amnesic stage may be is shown by the following case :—

Case 5.—G. S., a man of 32, came under our care on September 1, 1952. Two years before, bilateral apical pulmonary tuberculosis had been diagnosed but regarded as obsolete. However, during 1952 he began complaining of night sweats and general malaise and was accordingly admitted to hospital elsewhere, when radiography of his chest showed recent extension of the pulmonary lesion. At the end of August he began to complain of headache and became irrational and aggressive, and on August 30 he had a generalized convulsion. Lumbar puncture the next day yielded a fluid under normal pressure and containing 70 cells per c.mm. (90% lymphocytes), 100 mg. protein per 100 ml., sugar 73 mg. per 100 ml., and chlorides 680 mg. per 100 ml. The following day he was transferred to the Military Hospital for Head Injuries, Wheatley.

On admission there he was feverish but there was no stiffness of the neck. Three discrete oval or circular patches of choroiditis were seen in the right eye, he was a little tremulous, and had a mild degree of slurring dysarthria, but no other abnormal physical signs. Mentally, he was aggressive, suspicious, and confused. At night he became very irrational and noisy and was incontinent of faeces. Nevertheless, he was correctly orientated in time and space, his memory for past events was good, and he was able to retain seven digits forward and four backward without difficulty. Radiography of the chest confirmed the presence of bilateral pulmonary tuberculosis, and lumbar puncture yielded a fluid containing 163 cells per c.mm. (94% lymphocytes), 150 mg. protein, 40 mg. sugar, and 710 mg. chlorides per 100 ml. Examination of smears of the cerebrospinal fluid showed fragments of acid-fast material which were thought to be tubercle bacilli. A bromide blood-cerebrospinal fluid permeability test was set up (Taylor, Smith, and Hunter, 1954).

A provisional diagnosis of tuberculous meningitis was made and treatment begun with intrathecal and intramuscular injections of streptomycin. After the bacteriological report was received intrathecal tuberculin was also given. In spite of this, he grew worse. He developed retention of urine and the dysarthria and tremor grew more marked. Mentally he also deteriorated. He became euphoric and fatuous and would chatter to himself for hours, while psychological testing revealed gross defects of intellect and concentration. In spite of this, he remained correctly orientated and no serious defect in his powers of memorizing could be demonstrated.

It was by now apparent that the mental picture was very different from that usually seen in established cases of tuberculous meningitis ; moreover, the lack of response to specific chemotherapy, the results of serial bromide tests, and of pneumoencephalography, were all against this diagnosis. The original smears of the cerebrospinal fluid were therefore restained and re-examined, and it was established that the acid-fast fragments were artefacts. At the same time the Wassermann and Kahn tests were found to be strongly positive in blood and cerebrospinal fluid. The diagnosis of tuberculous meningitis was accordingly rejected in favour of general paresis. Subsequent events left no doubt that this was the correct diagnosis.

In this case the finding of a predominantly lymphocytic meningitis accompanied by choroiditis and mental changes in a man with established pulmonary tuberculosis strongly favoured a diagnosis of tuberculous meningitis. This diagnosis was first seriously questioned when it was appreciated that the pattern of the mental disorders was an exact reversal of the characteristic pattern of tuberculous meningitis in that orientation and memory were relatively well preserved in the face of gross disorders of intellect.

The fact that the mental picture in tuberculous meningitis is sufficiently constant to have diagnostic importance does not imply that it is unique. On the contrary, it is in many respects very similar to that seen in a variety of conditions. In particular, the sequence of events as described here bears an obvious resemblance to that following blunt head injuries of moderate and severe degree. An analogy can be drawn between what we have called the " confusional state " and the state of " traumatic delirium " ; and between the " amnesic state " of tuberculous meningitis and the " traumatic confusional state " (Symonds, 1949). Moreover, in both conditions the patient is left with a permanent amnesia for the period of confusion and with some degree of retrograde amnesia (Russell, 1935 ; Russell and Nathan, 1946).

But on closer comparison the differences appear only less striking than the resemblances. Thus, during the confusional state of tuberculous meningitis the patient shows none of the agitation, overactivity, and aggression seen in traumatic delirium and, for that matter, in many other acute organic confusional states. The severe mental confusion is accompanied and to some extent masked by profound somnolence—indeed, the depth of sleep exhibited by the patient at one moment, compared with the intensity of his reaction when stimulated the next, is a striking characteristic of tuberculous meningitis. In this respect the typical delirium also contrasts strongly with the perpetual, silent, struggling delirium, " le mutism furieux " (Rilliet and Barthez, 1884) of acute purulent meningitis.

The amnesic state of tuberculous meningitis resembles the traumatic confusional state in that disorientation in time and space, gross defects in memorizing, and a tendency to confabulation are common to both, as are the stages by which the patient recovers his memory (Martin, 1937) and orientation (Paterson and Zangwill, 1944). But whereas in the traumatic confusional state the defect in memorizing is accompanied by severe impairment of other intellectual functions—by " a basic confusion of thought " (Symonds, 1949)—in tuberculous meningitis the defect in memorizing is out of proportion to the intellectual loss as a whole. A patient may thus be capable of doing complex problems in mental arithmetic quickly and accurately (Case 3), or be the acknowledged draughts champion of his ward (Case 4) at a time when he is still incontinent and totally unable to recognize his doctors or to remember the time of year or the whereabouts of his hospital. There appears also to be a difference in quality between the amnesic state of tuberculous meningitis and such organic dementias as acute alcoholic intoxication, and the acute confusional stage of typhus and general paresis. The difference between the mental picture of tuberculous meningitis and that of general paresis has already been exemplified (Case 4). In tuberculous meningitis patients are seldom, if ever, grossly deluded or grandiose. They may fabricate stories of their past, but the incidents they recount are associated with actual past events and lack the " ego-inflating " quality noted by von Stockert (1943) in typhus. Though they lack insight and are commonly either slightly euphoric or sullen in their attitude, they are not elated or unduly talkative, nor over-emotional and subject to rapid changes in mood.

The difference between the mental disturbances consequent on tuberculous meningitis and those that follow a serious head injury become most striking when the permanent residua are considered. In both conditions amnesia for the period of confusion coupled with some degree of retrograde amnesia is the rule. But after head injury the relationship between the length of the post-traumatic amnesia and the permanent loss of intellectual acumen is so close that the duration of the post-traumatic amnesia has proved a valuable guide to the ultimate prognosis (Symonds and Russell, 1943 ; Russell and Nathan, 1946). In tuberculous meningitis, on the other hand, an amnesic period lasting for months has proved perfectly compatible with full intellectual recovery. So, too, with the permanent retrograde amnesia. After recovery from tuberculous meningitis the permanent retrograde amnesia is usually measured in days and often in weeks or months, and, together with amnesia for the active stage of the illness, forms the only detectable mental deficit in an otherwise perfect recovery. By contrast, the retrograde amnesia following head injury is commonly measured in seconds or minutes (Russell, 1935), while retrograde amnesias of more than a few hours' duration are not only exceptional, but are probably always associated with some permanent defect in mental function other than the amnesia (Symonds, 1949).

Finally, we have never seen the syndrome of post-traumatic dementia (Symonds, 1949) or traumatic psychasthenia (Mapother, 1937). One patient complained for some months of a tendency to undue fatigue, and the Service patients, who receive pensions, have, as a whole, been slower to return to full-time work than have the civilians. But the great majority of our patients have ultimately not only returned to work but have done so with all their old efficiency, while measurable defects in intelligence,

personality changes and temper tantrums, post-meningitic headaches, and epilepsy are conspicuous by their absence. The quality of recovery is, in fact, as good as that seen after successful treatment of pneumococcal meningitis (Smith, Cairns, and Duthie, 1946). This is the more remarkable when it is remembered that some patients suffered from severe systemic tuberculosis in addition to the meningitis, and that others became totally and permanently deaf from the streptomycin.

One other condition that must be considered is Wernicke's encephalopathy. The main features of this syndrome have been summarized as " loss of appetite, vomiting, nystagmus, diplopia, palsy of external ocular muscles, apathy or apprehension, loss of memory, disorientation, confabulation, and coma " (*Lancet*, 1952). If severe generalized wasting is added, it becomes an accurate outline of the clinical picture seen in any moderately severe case of tuberculous meningitis. Fuller descriptions of the mental changes in Wernicke's encephalopathy only emphasize the likeness (Phillips, Victor, Adams, and Davidson, 1952). Moreover, mental recovery, when it occurs, appears to follow much the same pattern as in tuberculous meningitis and to be complete except for amnesia for the period of confusion (De Wardener and Lennox, 1947). It thus appears that in quality, pattern of recovery, and concomitant physical findings the mental disturbances of tuberculous meningitis bear a closer resemblance to those of Wernicke's encephalopathy than to those of head injury, of acute intoxications, or of other intracranial infections.

Discussion and Conclusions

In brief, it may be said that the chief characteristic of the mental disturbances in tuberculous meningitis is a disproportion between the disorder of memory and that of other intellectual faculties. Early in treatment—that is, during the confusional state—this disproportion is not obvious because the gross failure of retentive memory is masked by semi-stupor or, more rarely, by frank delirium with hallucinations. But as the illness runs its slow course it becomes apparent that recovery of the memory defect lags farther and farther behind that of other intellectual functions until, in the end, the patient is left with a profound amnesia for much of his illness, and for the weeks or months preceding it, as his only permanent deficit.

It is tempting to try to correlate these mental changes with the pathological findings. It is notorious that in tuberculous meningitis the brunt of the disease falls on the base of the brain and particularly on the more anterior of the basal cisterns, the cisternae chiasmatica, interpeduncularis, et ambiens. In untreated cases the pathological changes are not limited to this site : the vessels over the convexity of the hemispheres are studded with tubercles, the brain itself may be oedematous, and some degree of infarction of brain tissue is the rule. In such cases the patients have usually been in profound coma for many days before they died.

But just as the stupor and general confusion of the moderately advanced, untreated case yields under treatment and is succeeded by the amnesic state, so, too, the pathological picture changes. In many of those cases that come to necropsy after a period of deadlock lasting for weeks, the inflammatory process is found to be virtually limited to the more anterior of the basal cisterns : the cisternae chiasmatica, interpeduncularis, et ambiens are choked with dense tuberculous exudate, while the cisternae pontis et magna show nothing more than a little thickening of the meninges. It is undoubtedly this exudate that, by virtue of its anatomical distribution, gives rise to many of the characteristic clinical findings ; for example, the communicating hydrocephalus, the optic atrophy, and, probably, the common sixth and third cranial nerve palsies (Cairns and Smith, 1952, figs. 117 and 118). This inflammatory process directly involves the floor of the third ventricle, and well marked hypothalamic disturbances complete the syndrome. In the Oxford series these disturbances have included hypertension (e.g., Case 2), glycosuria, anorexia or bulimia, hypo- or hyper-thermia, disturbances of sleep rhythm, diabetes insipidus, and Fröhlich's syndrome.

The correlation between the physical and pathological findings is thus unequivocal, and the question must be faced of whether or not there is any justification for attributing the mental picture to the same pathological changes.

There is a certain amount of circumstantial evidence to support this hypothesis. In the first place, the typical mental picture is not seen in other intracranial infections, such as general paresis, where the chief pathological changes are found in the substance of the cerebral hemispheres rather than in the hypothalamus and at the base of the brain (e.g., Case 5). Secondly, in those three cases already referred to that differed so markedly from our other fatal cases in that consciousness was fully preserved until shortly before death, the pathological findings showed an almost exact reversal of the typical pattern. In these three cases, and in these three only, the cisterna magna was obliterated by tuberculous exudate while the anterior basal cisterns were virtually clear.

Thirdly, there is the unmistakable correspondence between the intensity of the mental changes and that of the inflammatory process. This is best seen when intrathecal tuberculin is used in treatment (e.g., Case 4). During the tuberculin reaction the tuberculous lesion becomes hyperaemic and oedematous. This access of inflammation reaches its height about 24 hours after the injection and then subsides. The exacerbation of the mental disturbances follows exactly the same course, and this has been seen in cases where necropsy showed that active tuberculous disease was limited to the anterior basal cisterns.

Finally, there is an obvious analogy between tuberculous meningitis and Wernicke's encephalopathy. Not only are the physical and mental pictures in the two conditions remarkably alike, but in both the main pathological process is characteristically situated in, or in immediate relation to, the floor of the third ventricle and midbrain. Campbell and Russell (1941), when discussing the correlation between the clinical and pathological abnormalities of Wernicke's encephalopathy, comment on " the apparent fact that lesions situated as in Wernicke's disease can disorganize mental function ". Recently renewed interest has been shown in the part played by the diencephalon and brain-stem in the maintenance of consciousness (Cairns, 1952), and circumscribed lesions of the diencephalon have been shown to produce mental changes in man (Gillingham, 1953) and in animals (Sherwood, 1953).

Such evidence as we have that the mental changes in tuberculous meningitis are directly related to the characteristic anatomical lesion is, at the best, no more than suggestive. Nor is this any place to attempt to discuss the inter-relationship of different parts of the brain in regard to mental function. Nevertheless, we venture to present these observations on the mental changes in tuberculous meningitis in the hope that they may form a small contribution towards the delineation of the various patterns of mental disturbance associated with relatively clear-cut pathological lesions.

Summary

The mental disorders seen in tuberculous meningitis have been studied in adult patients both during the illness and after recovery.

The characteristic pattern of mental disorders seen once the full clinical picture has developed is described, together with variations in this pattern.

Three separate mental states are distinguished: the confusional state, the amnesic state, and the post-recovery state.

The chief characteristic of the mental changes is the predominance of the disorder of memory over the other intellectual deficits. This is seen most clearly in the amnesic and post-recovery states.

The pattern of recovery from the confusional and amnesic states is described.

The pattern of the mental disorders in tuberculous meningitis is compared with that seen in other organic dementias, notably that following head injury. It is pointed out that the picture in tuberculous meningitis is sufficiently characteristic to have diagnostic importance.

The possible relation between the mental disturbances of tuberculous meningitis and the characteristic pathological lesion is briefly discussed.

References

Barlow, T. (1899). *A System of Medicine*, ed. Allbutt. Macmillan, London.
Cairns, H. (1952). *Brain*, **75** 109.
——, Smith, H. V. (1952). In *Modern Practice in Tuberculosis*, ed. Sellors, T. Holmes, and Livingstone, J. L., Vol. 2, ch. 16. Butterworth, London.
——, Taylor, M. (1949). *Proc. roy. Soc. Med.*, **42**, 155.
Campbell, A. C. P., and Russell, W. R. (1941). *Quart. J. Med.*, **10**, 41.
De Wardener, H. E., and Lennox, B. (1947). *Lancet*, **1**, 11.
Gillingham, F. J. (1953). Personal communication.
Gow, A. E., and Scott, R. B. (1950). In *A Textbook of the Practice of Medicine*, ed. Price, F. W., 8th ed. Oxford University Press, London.
Gowers, W. R. (1893). *A Manual of Diseases of the Nervous System*, 2nd ed., Vol. 2. Churchill, London.
Henderson, D. K., and Gillespie, R. D. (1936). *A Textbook Psychiatry*, 4th ed. Oxford University Press, London.
Jolliffe, N., Wortis, H., and Fein, H. D. (1941). *Arch. Neurol. Psychiat., Chicago*, **46**, 569.
Korsakoff, S. (1889). *Rev. Philos.*, **28**, 501.
Leading Article (1952). *Lancet*, **2**, 1120.
——Personal Papers (1953). *Ibid.*, **1**, 1196.
Mapother, E. (1937). *Brit. med. J.*, **2**, 1055.
Martin, J. P. (1937). *Ibid.*, **2**, 1061.
Osler, W. (1892). *The Principles and Practice of Medicine*, 1st ed. Young J. Pentland, Edinburgh.
Paterson, A., and Zangwill, O. L. (1944). *Brain*, **67**, 54.
Phillips, G. B., Victor, M., Adams, R. D., and Davidson, C. S. (1952). *J. clin. Invest.*, **31**, 859.
Rilliet, F., and Barthez, E. (1884). *Traité clinique et pratique des Maladies des Enfants*, 3rd ed. Alcan, Paris.
Russell, W. R. (1935). *Lancet*, **2**, 762.
——(1952). *Poliomyelitis*. Edward Arnold, London.
——, Nathan, P. W. (1946). *Brain*, **69**, 280.
Sherwood, S. L. (1953). Personal communication.
Smith, H. V. (1953). *Proc. roy. Soc. Med.*, **46**, 588.
——, Cairns, H., and Duthie, E. S. (1946). *Lancet*, **1**, 185.
——, and Vollum, R. L. (1950). *Lancet*, **2**, 275.
Stockert, F. G. von (1943). *Dtsch. med. Wschr.*, **69**, 506.
Symonds, C. P. (1949). In *Injuries of the Brain and Spinal Cord and their Coverings*, ed. Brock, S., 3rd ed. Baillière, Tindall and Cox, London.
——, Russell, W. R. (1943). *Lancet*, **1**, 7.
Taylor, L. M., Smith, H. V., and Hunter, G. (1954). *Lancet*, **1**, 700.
Trousseau, A. (1868). *Lectures on Clinical Medicine*, Vol. 35, p. 453. New Sydenham Society, London.
Whytt, R. (1768). *Observations on the Dropsy in the Brain*. Balfour, Edinburgh.
Williams, M. (1953). *Journal of Neurology, Neurosurgery and Psychiatry.*, **16**, 14.
Wilson, J. A. (1844). *Lancet*, **2**, 218.

J. Neurol. Neurosurg. Psychiat., 1954, **17**, 183.

REPETITIVE DISCHARGES FROM HUMAN MOTOR NERVES AFTER ISCHAEMIA AND THEIR ABSENCE AFTER COOLING

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The phenomena which occur in nerves in the post-ischaemic state may be those observed subjectively as paraesthesiae, or those of which objective evidence is provided by the electromyogram as repetitive muscle action-potentials. Both are believed to be due to iterative discharges occurring in the nerve, either spontaneously or in response to action currents evoked by normal or electrical stimuli. In both groups, however, despite many ingenious experiments, authors have disagreed on the site of origin of the repetitive discharges. The purpose of the present study was to seek further evidence on this point, and to investigate the possibility that similar discharges occur during cooling and the subsequent return of the nerve to normal temperature.

Post-ischaemic paraesthesiae were discussed by Reid (1929, 1931), who thought that they arose in the sensory end-organs. Lewis, Pickering, and Rothschild (1931), Bazett and McGlone (1932), and Zotterman (1933) also observed them but thought that they arose in the nerve fibres themselves. A technique commonly used to study this problem is to apply two inflated cuffs to a limb, one above the other, deflating the proximal cuff first, so that the circulation returns only to the segment of nerve beneath it. With this method Merrington and Nathan (1949) reported typical paraesthesiae, and Kugelberg (1946) recorded repetitive muscle action-potentials. They concluded that the site of origin of these phenomena was in any segment of nerve recovering from ischaemia. Weddell and Sinclair (1947) also found paraesthesiae under these conditions, but considered them to be less intense than when the circulation was restored to the whole limb. They concluded that it is the return of the blood supply to nerve-endings which produces post-ischaemic paraesthesiae. Magladery, McDougal, and Stoll (1950), also using double cuffs, recorded repetitive muscle action-potentials while the distal cuff was still in place. They argued that a cuff on the forearm would allow blood to leak past, and hence the repetitive muscle action-potentials could not be assumed to be due to impulses arising in the segment of nerve under the proximal cuff. This criticism was answered by Kugelberg and Cobb (1951) who showed that release of pressure, just sufficient to permit a palpable pulse at the wrist for six minutes, was insufficient to cause repetitive responses, though they occurred readily when the circulation was completely released.

Another experimental technique, which might have been expected to give a definite answer to the problem, was to occlude the circulation in an amputation stump. Following such an occlusion Weddell and Sinclair found no paraesthesiae in the phantom limb, whereas two out of Merrington and Nathan's seven subjects reported paraesthesiae. The latter authors suggest that failure to obtain paraesthesiae in some cases is probably due to the practice of dividing nerves as high as possible during amputation. Thus, unless a cuff can be placed high on the stump, the nerve trunk may not be rendered ischaemic.

Localized compression of a segment of nerve without occlusion of the peripheral circulation has also been employed as a method of study. Again Merrington and Nathan found typical paraesthesiae, while Weddell and Sinclair reported none. The former authors made it clear that a greater length of nerve must be made ischaemic to cause paraesthesiae than that required to produce sensory loss. Recordings of muscle action-potentials after ischaemia of a short segment of nerve have not been reported.

The importance of this subject is more than merely academic for ischaemia is being used increasingly as a means of studying clinical problems (Bharucha, 1952; Marshall, 1952; Gilliatt and Wilson, 1953), so that accurate knowledge of the site of origin of these phenomena is required.

If a segment of nerve can be rendered ischaemic

without impairment of the circulation to the nerve endings, then positive phenomena occurring after ischaemia must arise in that segment of nerve. The original nerve clamp of Lewis and others (1931) was somewhat unpredictable in its action, but even so, in satisfactory experiments, no question of impediment to the peripheral circulation arose. The modified clamp (Marshall, 1953) is much more reliable, and any obstruction to the circulation can be confidently rejected. Hence, in the study reported here a nerve clamp was used to produce local ischaemia in nerve fibres. The effects during and after cooling the nerve were separately observed.

Methods

The observations were made on six healthy adult subjects.

The electromyographic recordings were made through a coaxial needle electrode inserted into the first dorsal interosseous muscle. The action-potentials were amplified by a differential amplifier with an adequate range of frequency response, and displayed on one beam of a double-beam cathode ray oscillograph. The other beam was fed with a time scale giving intervals of 1 and 10 m. sec., derived from a crystal oscillator.

Cathodal stimulation of the ulnar nerve was applied as high in the upper arm as possible or at the wrist. The voltage pulse of the stimulus had an exponential decay with a time constant of 20 μ sec., and the stimulus was made supra-maximal, as judged from the amplitude of the summated muscle action-potential at the beginning of the experiment. The stimulus was triggered once per second by the time scale, at a point indicated on it.

Ischaemia of the limb was produced by a sphygmomanometer cuff, 12·5 cm. wide, inflated to 200 mm. Hg, placed around the arm immediately above the elbow, and below the point of stimulation of the nerve in the upper arm.

Ischaemia of a segment of the ulnar nerve immediately above the elbow was produced by a modified nerve clamp (Marshall, 1953) 12·5 cm. long ; it was inflated to 100 mm. Hg, this pressure having been found to give rise to ischaemic and post-ischaemic changes without any impairment of the general circulation to the limb.

Cooling of a segment of the ulnar nerve at about the same level was obtained by placing the flexed elbow in a mixture of ice and water at 0 to 1° C., the electrical stimulus being applied proximal to the cooled area.

Results

All the illustrations are from experiments on the same subject ; there are small variations in latency from subject to subject but those illustrated are typical and are quoted alone for simplicity.

Observations before Ischaemia or Cooling.—Following a stimulus in the upper arm there is a latent period of about 12 m. sec. before the occurrence of the primary response in the first dorsal interosseous muscle (Fig. 1a). At about 25 m. sec. a further, much smaller, response occurs, which is the F wave of Magladery and others (1950) ; this is extremely variable in its occurrence and may be barely visible or relatively large and sharp ; in any subject, for a given electrode placement, it has several forms, each of which may be recognized by the wave shape. The limited number of constant forms of response suggests that each is the product of one motor unit, the form and size depending on the relation of this to the needle electrode.

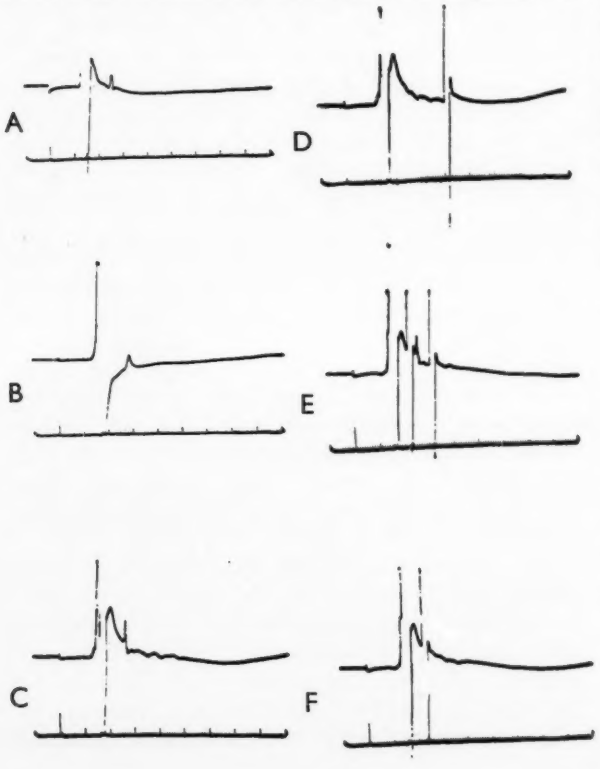

FIG. 1a.—A single cathodal stimulus to the ulnar nerve high in the upper arm gives rise to a primary response from first dorsal interosseous muscle with a latency of 12 (·2) m. sec. followed by an F wave with a latency of 24 (·5) m. sec.

FIG. 1b.—After 17 min. ischaemia, produced by an inflated cuff on the arm, the primary latency has increased to 13 (·5) m. sec., and the F latency to 27 (·5) m. sec.

FIG. 1c.—The cuff was released immediately following B, and 2 min. later a small repetitive response begins and is seen in all subsequent records, up to seven minutes.

FIG. 1d.—After a further 2 min. a high-voltage spike occurs following each stimulus, at first with a latency of 40 m. sec.

FIG. 1e.—The latency of this spike decreases and it is shortly followed by another identical spike. In this example the F wave lies between the two spikes.

FIG. 1f.—The second spike no longer occurs and the latency of the first has fallen to 22 m. sec.; it also ceases shortly afterwards.

Time-scale for all figures 1 and 10 m. sec. Stimulus at 10 m. sec. (For calibration see Fig. 3).

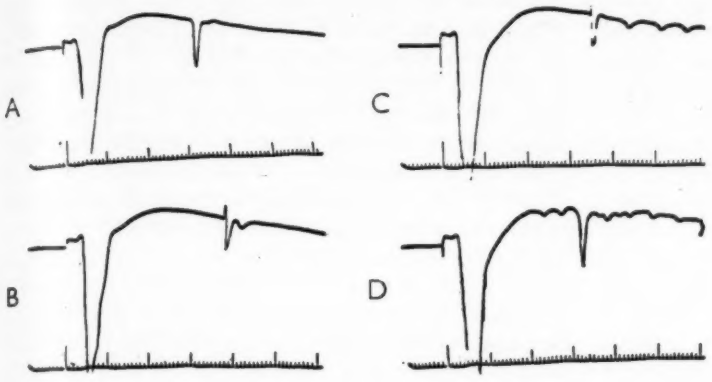

FIG. 2a.—As for 1a, but the stimulus applied to the ulnar nerve at the wrist. The primary latency is 2 (·8) m. sec. and the F latency 32 m. sec.

FIG. 2b.—After inflation of the cuff on the arm for 14 min. there is no change in the primary latency, while that of the F wave has increased to 38 m. sec.

FIG. 2c.—About 2 min. after release of the cuff a repetitive response occurs, at first following the F wave.

FIG. 2d.—Several minutes later, when the F latency has returned to its original value, repetitive responses occur both before and after the F wave.

Note the two distinct forms of F wave.

Following stimulation at the wrist the primary response has a latency of about 3 m. sec. while the F wave is delayed to about 32 m. sec. (Fig. 2a).

Observations after Ischaemia Produced by a Cuff.—The events which occur during and after occlusion of the circulation to the whole limb distal to a cuff on the arm are illustrated in Figs. 1 and 2. Fig. 1a shows the response to stimulation of the ulnar nerve above the cuff before ischaemia. After ischaemia for 17 min. the latencies of the primary response and F wave have become 13 (·5) and 27 (·5) m. sec. respectively (Fig. 1b); these are smaller increases than were obtained in some of the subjects for comparable durations of ischaemia, up to 4·5 m. sec. for the primary response being noted.

Two minutes after release of the cuff at 17 min. small repetitive responses begin, shown in Fig. 1c following the F wave, whose latency has fallen to 26 m. sec. After a further two minutes a high voltage triphasic action-potential appears, and recurs after every stimulus; at first its latency is 40 m. sec. (Fig. 1d), but this steadily drops and it is shortly followed by a second identical spike seen in Fig. 1e with the F wave between them. After being evoked by a number of successive stimuli the second spike drops out (Fig. 1f) and later the first also. During the whole of this time the initial small response has continued, but finally ceases about seven minutes after release of the cuff.

Fig. 2 illustrates the results of stimulation at the wrist; the subject is the same as in Fig. 1 but the occasion different.

In Fig. 2a, before ischaemia, the latency of the primary response is 2 (·8) m. sec. and that of the F wave 32 m. sec. After inflation of the cuff on the arm for 14 min. there is no detectable change in the primary latency but that of the F wave has increased to 38 m. sec. (Fig. 2b). During this experiment two forms of F wave consistently appeared as shown in a and b.

Following release of the cuff repetitive responses appear from about the middle of the second minute to the eighth; at first (Fig. 2c) they only follow the F wave, but later occur both before and after it (Fig. 2d) at a time when the F latency has returned to its initial value.

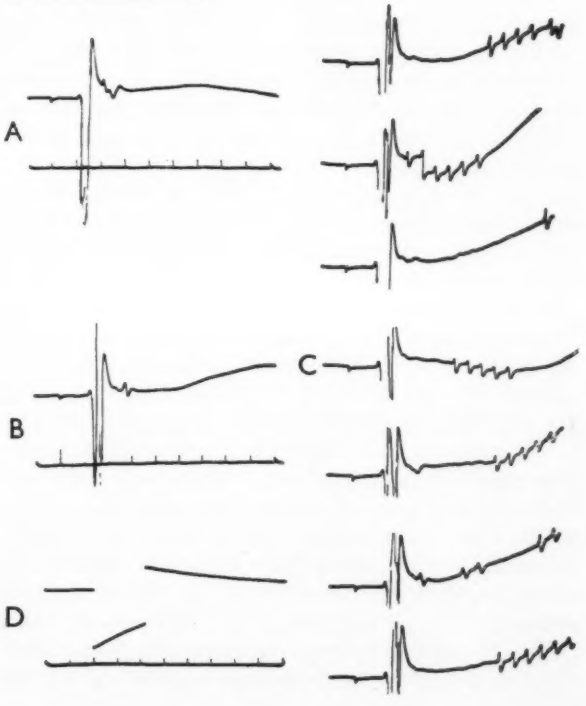

FIG. 3a.—As for Fig. 1a.

FIG. 3b.—After inflation of a nerve-clamp on the ulnar nerve above the elbow for 19 min. both latencies are slightly increased.

FIG. 3c.—Following a release of the clamp at 20 min. a repetitive response occurs from about the first to seventh minute. Seven successive sweeps at 1 sec. intervals show the great variability in timing of the response.

FIG. 3d.—Calibration = 1 m.V.

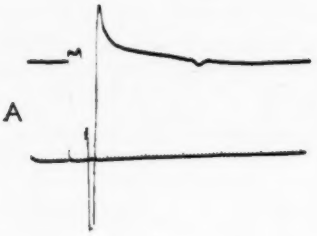

FIG. 4a.—As for Fig. 2a.

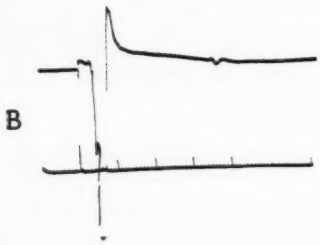

FIG. 4b.—The nerve-clamp has been inflated for 18 min. and the F latency is slightly increased.

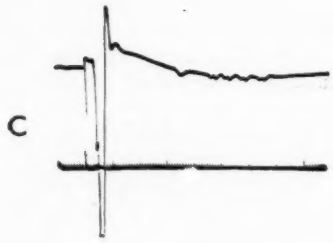

FIG. 4c.—Several minutes after release of the clamp repetitive discharges occur after the F wave. They were never seen before it.

Observations after Ischaemia Produced by a Nerve-clamp.—When the clamp was applied to the ulnar nerve at a pressure of 100 mm. Hg no impediment to the arterial supply to or venous return from the limb could be detected. Stimulation was carried out exactly as in the previous experiments and typical results are illustrated in Figs. 3 and 4. In Fig. 3a, before inflation of the clamp, the primary response has a latency of 11 m. sec. and the F wave, which is not well differentiated from it, of 23 m. sec.

After compression of the nerve for 19 min. the primary latency has risen to 12 m. sec. (Fig. 3b) and the F latency to 25·5 m. sec. In all the clamp experiments the changes in latency were less than for the cuff experiments on the same subjects.

The pressure was released at 20 min. and repetitive responses began about one minute later. Fig. 3c shows the results of seven successive stimuli, in which it can be seen that the time distribution of the responses varies considerably and in no predictable manner, although the constancy of wave form suggests that it is the same unit firing in every case.

On the occasion when this same subject was used for the clamp experiment with stimulation at the wrist, both the F wave and repetitive responses were small, though perfectly clear and consistent. Fig. 4a shows a primary latency of 2 (·8) m. sec. and an F latency of 33 m. sec. before inflating the clamp. After compression for 18 min. the primary latency is unchanged (Fig. 4b) and the F latency has risen to 35 m. sec. Release of the clamp at this time was followed for a longer interval without repetitive responses than in the cuff experiments, but they then recurred for several minutes, up to eight minutes after release of the clamp. At no time were they seen to occur before the F wave (Fig. 4c), or its expected time when it was not actually measurable.

Observations during and after Cooling of a Nerve Segment.—By placing the flexed elbow in ice-water a segment of the ulnar nerve in the region of the elbow, by reason of its superficial position, was subjected to cold. This segment was approximately the same in length as that compressed by the cuff and clamp but possibly a little more distal. As the sites of stimulation and recording were the same as during ischaemia, the experimental conditions were nearly identical.

Fig. 5a shows the response to stimulation in the arm before the elbow was inserted in the ice; the

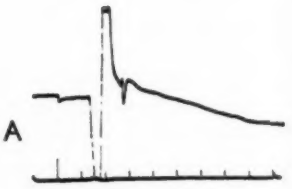

FIG. 5a.—As for Fig. 1a. Primary latency 12·5 m. sec.; F latency 26·5 m. sec.

FIG. 5b.—The flexed elbow has been placed in ice-water to cover about 12 cm. from the elbow proximally. Stimulation of the ulnar nerve in the upper arm during the 30-min. period of immersion causes no unusual responses, while the latencies rise to 18·5 and 35 m. sec.

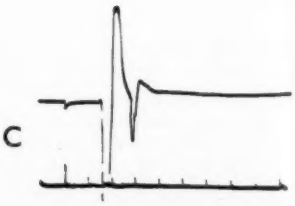

FIG. 5c.—Stimulation at frequent intervals during the 20 min. following removal of the elbow from the ice-water caused no repetitive discharge.

primary latency is 12·5 m. sec. and the F latency 26·5 m. sec. Stimulation is continued at 1 sec. intervals while the elbow remains in the ice for 30 min. (the period varying from 10 to 30 min. in the different trials). During cooling no major change is noted in the muscle action-potential except an increase in primary latency to 18·5 m. sec. and in F latency to 35 m. sec. (Fig. 5b).

The elbow is then removed from the ice and stimulation continued at intervals to 20 min. The latencies return to the initial values more slowly than after ischaemia, being still increased at 15 min. (Fig. 5c). At no time in any subject was there any suggestion of a repetitive response. In the experiment illustrated immersion in ice-water was continued for longer than in any other and the changes in latency are more extreme than in them ; the rate of recovery is correspondingly slower.

Stimulation at the wrist was not performed in view of the absence of any repetitive response.

Discussion

The cuff experiments were a repetition of the work of several authors and were done to provide a control with which to compare the nerve-clamp and cooling experiments ; they do, however, bring out several points of importance in the discussion of this subject.

The variations in form of the F response have already been mentioned, with reasons for supposing that they must be due to the discharge of different units having varying relationships to the needle. As the F wave is always smaller and briefer than the primary response it is evident that it can only represent a fraction of the total units within range of the needle ; which unit actually fires is presumably determined by fluctuations in excitability within the available neuron pool.

The repetitive responses during post-ischaemia show the same, or an even wider, variation in form, but here again it is usually possible, with the more sharply defined examples, to recognize that at any time it is probably only one motor unit which is firing, or sometimes two or three ; this is particularly clearly seen in Fig. 1, which shows the largest response in the whole series in great contrast with the other response in the same figure, which presumably occurred in a more distant unit.

This figure also shows clearly the possibility of changes in latency of the repetitive response, which in this case at least became shorter throughout the period during which this response occurred though with a not quite constant progression. By contrast, the timing of the repetitive response in Fig. 3c shows a completely random scatter.

The importance of these considerations is that comparisons between the responses to different experimental techniques cannot be made on the basis of their clarity ; the cuff may be more evocative of a repetitive response than the clamp but the differences between Figs. 1 and 3 are not evidence for it. Similarly, care must be exercised in making deductions from the latency of the repetitive response, which is subject to wide variation, though on the whole tending to shorten during the period of recovery.

When the nerve-clamp was used the pulses in the forearm were full and free, blanching of the nail-bed on pressure was followed by an immediate return of the red blush, and the veins showed no distension. Furthermore, the ischaemic and post-ischaemic subjective changes were confined to the ulnar fingers ; one subject, deluded by the lack of such changes in the index finger, was surprised to find, after compression for only 17 min., that he had complete motor nerve block to the first dorsal interosseous muscle. It can be assumed, therefore, that the properly positioned nerve-clamp renders ischaemic a segment of the ulnar nerve which is probably about the same length as that of the clamp and certainly does not extend to the nerve endings. Comparison of the changes in latencies of the primary response and F wave in the cuff and clamp experiments is consistent with this view, but they could be due to different degrees of coincident cooling of the hand and forearm.

It is clear that in the clamp experiments the repetitive responses must have arisen in the length of nerve under the clamp, the only portion to have been ischaemic, and not at the myoneural junctions. Further evidence for the purely local nature of the ischaemia, and hence of the hyperirritability, is provided by the timing of the repetitive response. When the whole forearm has been ischaemic and a stimulus is applied to the ulnar nerve at the wrist repetitive responses might be expected to occur immediately following the primary response, and this was sometimes observed. On the other hand, when using a clamp at the elbow, a stimulus at the wrist would be applied to normal nerve and no immediate repetitive response could be expected, nor was it seen.

Although the three experimental techniques were as nearly similar as possible it was only after cooling that a repetitive response could not be seen at all. It seems unlikely that this absence was due to inadequate cooling, for the increase in latency of the primary response was about 50%. A possible explanation is that the changes in the nerve responsible for repetitive discharges take place more

slowly after cooling than after ischaemia. Thus, after cooling it required ten minutes or more for the latency of the response to return to its original value, whereas after ischaemia the average time was about five minutes. It may, therefore, be the relative rapidity of the changes in the nerve which causes spontaneous firing in the post-ischaemic state. In a somewhat similar experiment Pinelli and Buchthal (1953) kept the hand warm and recovery was then much more rapid, although the duration of cooling was one hour and its degree probably greater. Like us they did not notice any spontaneous or evoked repetitive response, in this case to the natural stimulus of voluntary muscular contraction.

A more probable reason is that ischaemia and cold have fundamentally different effects on nerve fibres. This would accord with the difference in the order of loss of sensory modalities (Sinclair and Hinshaw, 1951), and in the behaviour of the pain threshold (Marshall, 1953) which have been observed in ischaemia and in cooling of a nerve. The subjective changes after ischaemia and after cooling have also entirely different qualities.

It may be concluded, therefore, that the phenomena observed in nerves after ischaemia arise not in the nerve endings but in that segment of the nerve trunk which was rendered ischaemic. Interpretation of tests which use ischaemia produced by a cuff or by a clamp need to be made in the light of this fact. Cooling a similar segment of nerve does not produce these phenomena, possibly because the effects of cold and ischaemia on nerve fibres are fundamentally different.

Summary

Further evidence is presented on the site of origin of the repetitive discharge in (human) motor nerves following ischaemia, as revealed by the electrical discharge in muscle.

During the recovery period following ischaemia, produced by inflation of a pneumatic cuff round the arm, repetitive discharges are readily evoked in the first dorsal interosseous muscle by electrical stimulation of the ulnar nerve.

A similar result may be obtained by local pressure, exerted by a nerve-clamp on the same segment of the ulnar nerve, although, during compression, there is no evidence of interference with the general circulation of the forearm and hand.

It is concluded that the repetitive discharge arises in that segment of the nerve which has been ischaemic.

After a similar length of nerve has been cooled by immersion of the elbow in ice-water for up to 30 minutes no repetitive discharge can be evoked.

This supports the subjective evidence that the effects of ischaemia and cooling on nerve are qualitatively and probably fundamentally different.

Our thanks are due to Prof. Eric Kugelberg and Dr. P. A. Merton for helpful criticism and to Mr. H. B. Morton for his technical assistance, also to Dr. E. A. Carmichael, Director of the Neurological Research Unit, for his encouragement.

References

Bazett, H. C., and McGlone, B. (1932). *Arch. Neurol. Psychiat., Chicago*, **28**, 71.
Bharucha, E. P. (1952). *Clin. Sci.*, **11**, 233.
Gilliatt, R. W., and Wilson, T. G. (1953). *Lancet*, **2**, 595.
Kugelberg, E. (1946). *Brain*, **69**, 310.
——, and Cobb, W. (1951). *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 88.
Lewis, T., Pickering, G. W., and Rothschild, P. (1931). *Heart*, 16, 1.
Marshall, J. (1952). *Journal of Neurology, Neurosurgery and Psychiatry*, **15**, 242.
——(1953). *Clin. Sci.*, **12**, 247.
Magladery, J. W., McDougal, D. B., and Stoll, J. (1950). *Johns Hopk. Hosp. Bull.*, **86**, 313.
Merrington, W. R., and Nathan, P. W. (1949). *Journal of Neurology, Neurosurgery and Psychiatry*, **12**, 1
Pinelli, P., and Buchthal, F. (1953). *Electroenceph. Clin. Neurophysiol.*, **5**, 589.
Reid, C. (1929). *Quart. J. exp. Physiol.*, **19**, 127.
——(1931). *Ibid.*, **21**, 243.
Sinclair, D. C., and Hinshaw, J. R. (1951). *Brain*, **74**, 318.
Weddell, G., and Sinclair, D. C. (1947). *Journal of Neurology, Neurosurgery and Psychiatry*, **10**, 26.
Zotterman, Y. (1933). *Acta med. scand.*, **80**, 185.

J. Neurol. Neurosurg. Psychiat., 1954, **17**, 189.

ANGIOGRAPHIC DIAGNOSIS OF VERTEBRAL ARTERY THROMBOSIS*

BY

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The diagnosis of vascular lesions of the brain may be very difficult: clinicians frequently see cases in which the mode of onset and the clinical features suggest that a haemorrhage or thrombosis has occurred, and yet the later developments show that the symptoms have been due to a tumour. Conversely, there are cases in which the insidious onset and apparent progression of symptoms might reasonably be ascribed to a tumour, but further investigation reveals instead a vascular lesion. With increasing interest in the active treatment of some of these lesions, differential diagnosis becomes even more important. In the case of lesions of the cerebral hemisphere, carotid angiography has proved to be a valuable expedient, and it is usually possible to say on the basis of this comparatively simple procedure whether we are dealing with neoplasm, haemorrhage, or clot. For lesions below the tentorium, however, angiography of the vertebral system is less reliable: the technique is more difficult, and in cases of tumour or vascular occlusion, it might be dangerous.

There are, however, some circumstances under which carotid angiography demonstrates the vertebral system of arteries, and this report is concerned with two such cases, in both of which the basilar artery filled via the posterior communicating arteries owing to thrombosis of the lower parts of the vertebral system.†

Case Reports

Case 1.—The first patient was a man of 56 years with a very scanty history. His wife said that his mentality and character had been deteriorating for about 12 months. He was forgetful, irritable, and uninhibited and his manners became progressively more asocial. Apart from a pathological appetite, he had no physical symptoms until three months before admission when he began to have occasional attacks of giddiness and vomiting. On the day before admission to hospital he became very drowsy, and he was sent into hospital under suspicion of having a frontal lobe tumour. On admission he was drowsy and confused and had persistent hiccough. No focal neurological abnormalities were detected and there was no objective evidence of increased intracranial pressure. The blood pressure was 180/120 mm. Hg and the blood urea and blood sugar levels were normal. A carotid angiogram (see below) showed no evidence of tumour, and as the diagnosis was still uncertain a ventriculogram was done. This likewise showed no evidence of a tumour, but there were curious collections of air in the region of the incisura tentorii which persisted despite alteration in posture of the head. It was thought that this appearance might be due to subarachnoid pouch and the region was accordingly explored through a right occipital osteoplastic flap. No definite abnormalities were found and the patient died on the following day.

At necropsy, the diagnosis was immediately apparent: there was thrombosis of both vertebral arteries, the left posterior inferior cerebellar artery, and a recent clot in the basilar artery. All these vessels were markedly atheromatous, although the carotid system appeared to be normal. There was acute ischaemic softening of both cerebellar lobes and of the left side of the medulla; the cerebral hemispheres, basal ganglia, and brain-stem were all normal.

This case showed little of the common clinical features of vertebral or basilar occlusion but the history and examination were necessarily limited by the rapid terminal collapse. When the arteriogram was reviewed, I was struck by the fact that the upper part of the basilar artery was well filled from the carotid injection, and it seemed likely that this might be of diagnostic value in future cases.

Case 2.—The second patient was a woman, 52 years old, who had been known to have high blood pressure for five years. Four years before admission, there was an episode of acute pain in the neck which lasted for a week and then cleared up completely. For several weeks before she came into hospital she complained of recurrent numbness of the right little finger, each bout lasting two or three days. Two days before admission, she had an attack of giddiness while riding a bicycle. On the day of admission she woke up with acute vertigo and vomiting, and it was these symptoms which led to her being sent to hospital.

* Based on a paper read to the Society of British Neurological Surgeons in May, 1953.

† Since this paper was prepared, three further cases have been seen.

On admission, she was somewhat cyanosed and short of breath, and she looked ill. She was very excited, talking loudly in an uninhibited manner. The head was kept turned to the right but the neck was not stiff. The positive neurological abnormalities amounted to paralysis of conjugate lateral movements of the eyeballs with rapid rotatory nystagmus on looking to the right and upwards ; impaired sensation in the left trigeminal zone ; a left peripheral facial palsy ; a relative increase in the tendon reflexes in the right limbs, and slight ataxy of the left limbs. There was no evidence of increased intracranial pressure. The blood pressure was 180/120 mm. Hg.

These clinical features pointed to thrombosis of the left posterior inferior cerebellar artery with probable partial occlusion of the basilar artery. The patient was treated with heparin and nicotinic acid and rapidly improved. She was discharged from hospital at the end of two months with no neurological abnormalities except slight unsteadiness of gait.

Nine months later she was readmitted in a very similar attack characterized by excitement, dysarthria, rapid and irregular respiration, nystagmus, spastic weakness of the right limbs, and ataxy of the left limbs. On this occasion a carotid angiogram was done and in addition to the normal carotid circulation, the upper part of the basilar and the superior cerebellar arteries were visualized as in the first case (Fig. 1).

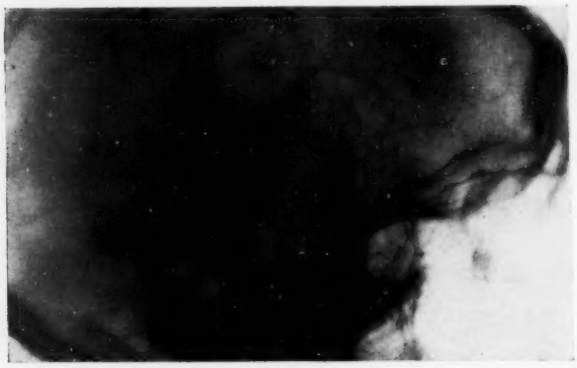

FIG. 1.—Carotid arteriogram of Case 2.

Again there was rapid improvement with medical treatment, and when seen one and a half years later she appeared to be well and had no residual neurological deficit except slight unsteadiness of gait. It was noted, however, that if her head was bent backwards, she complained of giddiness and nystagmus developed, features described by Biemond (1951) as being characteristic of obstructed circulation in the vertebral arterial system.

Comment

Filling of the basilar artery with contrast medium injected into the common carotid artery occurred in these two cases by way of the posterior communicating artery. If the vertebral or proximal part of the basilar artery is occluded, the contrast medium in the carotid system has less pressure to meet and the possibility of such reflex filling would be enhanced. In a series of 500 carotid angiograms I have seen filling of the basilar artery in only two other cases. The first was in a patient with thrombosis of the internal carotid artery. As the external carotid circulation could not take all the contrast medium, some of it flowed back in the common carotid artery and reached the basilar by way of the vertebral artery. Moniz (1940) and Krayenbühl and Richter (1952) have described similar cases. The second case was that of a child with bilateral subdural haematoma. A right carotid angiogram filled the whole intracranial arterial tree (Fig. 2), i.e., the vessels of

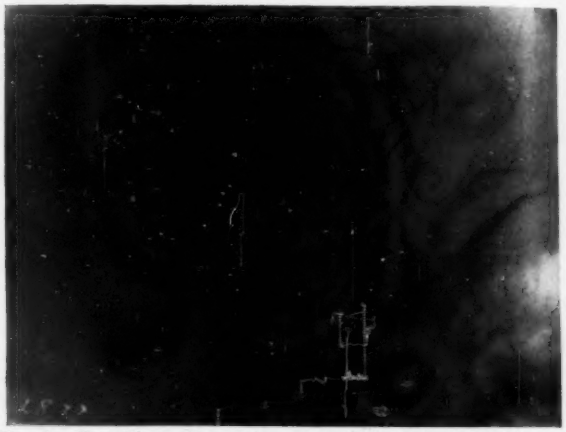

FIG. 2.—Carotid arteriogram in a case of bilateral subdural haematoma, showing good filling of the basilar artery and its branches.

the right and left cerebral hemispheres, as well as the basilar and vertebral arteries. Moniz has also described this finding in some cases of high intracranial pressure, and certainly the pressure was very high in our case. But as increased intracranial pressure could be excluded in the two cases reported above, it seems likely that when the basilar artery is visualized by carotid angiography some obstruction in the vertebral artery should be considered.

In many cases of thrombosis of the vertebral, posterior inferior cerebellar and basilar arteries, the clinical features are sufficient for the diagnosis. But in doubtful or obscure cases it is suggested that carotid angiography may prove helpful not only by excluding a cerebral tumour but also by demonstrating filling of the basilar artery.

Summary

Two cases are reported of thrombosis of the vertebral artery system in which carotid angiography filled the basilar artery via the posterior communicating artery.

REFERENCES

Biemond, A. (1951). *Brain*, 74, 300.

Krayenbühl, H., and Richter, H. R. (1952). *Die Zerebrale Angiographie*. Georg Thieme, Stuttgart.

Moniz, E. (1940). *Die Cerebrale Arteriographie und Phlebographie. Handbuch der Neurologie*, ed. Bumke, O. and Foerster, O., Ergänzungsserie II. Springer, Berlin.

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A CONTRIBUTION TO THE GENETICS OF GARGOYLISM

BY

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The first clinical description of this syndrome by Hunter (1917) was quickly followed by that of Hurler (1919). Later, Ellis, Sheldon, and Capon (1936) coined the name " gargoylism " because of the cephalic, facial, and thoracic grotesqueness reminiscent of the figures on the Cathedral of Notre Dame in Paris.

The fundamental defect, as stated by Jackson (1951), is twofold, namely, a chondro-osseous dystrophy together with the storage of an abnormal macro-molecular substance. Involvement of the skull, spine, ribs, and long bones, storage deposition in the reticulo-endothelial system and in widespread parenchymatous and connective tissue, lead to the clinical picture most characteristic of gargoylism. Since this picture is important in the diagnosis of cases by inference, it will be briefly described here.

Most authors agree that the head is enlarged with well marked supra-orbital ridges, a squat nose with depressed bridge, thick lips, strong teeth, a large tongue, apparently low-set ears, and a short neck. The eyes may or may not have corneal opacities. The hair is thick, especially on the scalp and eyebrows. The lower part of the thorax tends to flare and the spine is kyphotic. The abdomen appears large and is often herniated. There is hepatosplenomegaly but sometimes the liver, alone, is palpable. The genitalia are infantile in type. The long bones are stunted, with a variety of orthopaedic defects, the most noticeable of which is restriction of extension at the joints, particularly the fingers, elbows, and knees. A predisposition to infections of the respiratory tract is a noteworthy feature.

The mode of genetic inheritance is a matter of controversy, and some pedigrees indicate that a single, recessive, autosomal gene is responsible, whereas others implicate a gene which is a sex-linked recessive. Helmholz and Harrington (1931), Halperin and Curtis (1942), and Jackson (1951) support the former, whereas Wolff (1942), Njå (1945–46), and Millman and Whittick (1952) adhere to the latter view. Njå, indeed, equates the presence of clear corneae with sex-linked inheritance, and this paper describes a British family in which the findings lend support to Njå's equation.

Method of Investigation

Two living cases, the second of which was discovered when working through the pedigree of the first, were examined by the author, and all the family histories were obtained personally and in conjunction with a social worker. A great deal of time was spent on the latter aspect of the investigation, and family witnesses were cross-checked after the completion of a questionnaire carefully designed to eliminate leading questions. Family albums and photographs were inspected and, where permission was obtained, copies made. Throughout, one was impressed by the intelligence of the relatives and in no witness was this considered to fall below average.

The diagnosis in three cases rests on a clinical examination, in four on a combination of photographic and lay descriptive evidence, in one on both medical and lay description, and in the remaining four on lay description alone.

Case Reports

Case 1.—This boy (Fig. 2, IV, 12, and Fig. 1), with whom the investigation began, is a typical gargoyle, aged 9½ years. Pregnancy and labour were normal. Teething began at 6 months, walking at 1½ years, and speech at 1¼ years. The cranial circumference is increased and measures 22½ inches, the sagittal is 15½ inches and the lateral (ear-to-ear) 13 inches. The scalp hair is thick and coarse. The teeth are large and widely spaced.

FIG. 1

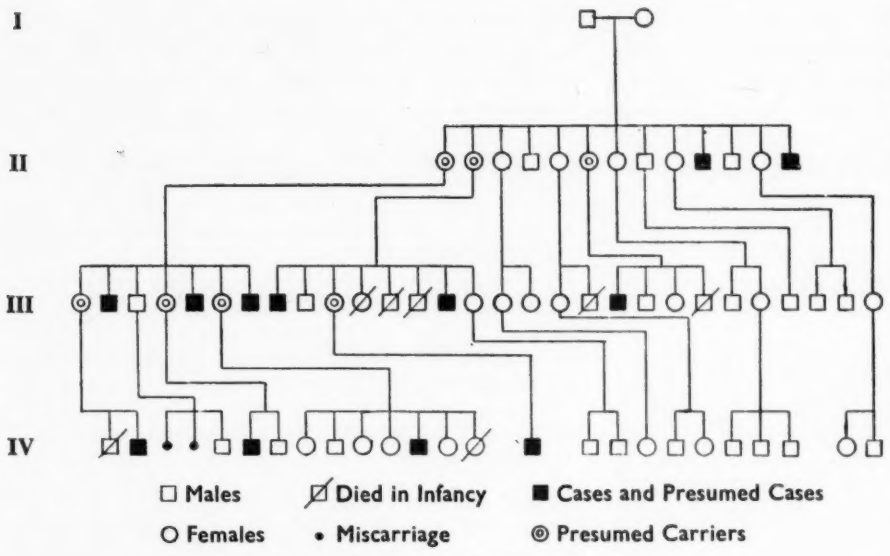

FIG. 2.—Pedigree of the affected family.

The mandible and the supra-orbital ridges are prominent, the latter bearing bushy hair. The infra-orbital areas are puffy and the cornea clear. The ear lobes are large and the nose broad with a somewhat depressed bridge. The neck is short and the shoulders hunched. At the level of the nipple the circumference of the chest is 28 inches, and at the umbilicus the protuberant abdomen measures 32½ inches. One scapula is considerably higher than its fellow, the liver is much enlarged, the spleen palpable, and the lower costal margin flared. The upper limb measures 14½ inches from the acromion to the radial styloid, and the lower 24 inches from the anterior superior iliac spine to the internal malleolus. The height is only 45 inches and the weight 78 pounds. The gait is waddling with a rigid, flat back, genu valgum, pes planus, and small patellae which are difficult to palpate. The genitals are poorly developed. The fingers, elbows, and knees are flexed, and extension in these joints is severely limited. The heart sounds are normal but the chest is very bronchitic and the child wheezes on moderate exertion. The skin is normal. His bodily development is rotund and, relatively, pyknic.

The boy is an imbecile and he would not cooperate in testing, and destroyed the test material. He is incontinent of urine and his habits are deteriorating.

Radiographs show an enlarged skull with an enlarged, deep, firmly lined sella turcica. The left coronal suture is a little open. The radii are somewhat deformed, the vertebrae ovoid with the first and second lumbar bodies basally hooked. The ribs are broadened in their anterior aspects.

Case 2.—This child (Fig. 2, IV, 15), aged 8¼ years, is also a gargoyle, although his bodily configuration differs considerably from that of his half-cousin, Case 1. Pregnancy and labour were normal. Teething began at 4 months but decay was an early feature. He began to walk at 1 year 2 months and the first attempt at speech was made at 1 year. The cranial circumference is increased at 22 inches, the sagittal is 14 inches, and the lateral 13 inches. There are temporal bulges and the scalp hair is coarse. The teeth are very carious, the tongue enlarged and fissured, the lips thick, and the mouth a little open. The mandible and supra-orbital ridges are prominent, the latter bearing bushy hair. The eyes are blue, the lashes long, and there is hypertelorism. The corneae are clear. The ears are low placed with large lobes, the nose squat, and the bridge depressed. The circumference of the chest at the nipple is 27 inches and the abdomen only 26 inches at the umbilicus. The liver is enlarged four fingerbreadths, but the spleen is not palpable. The upper limb measures 15 inches and the lower 26¼ inches. His height is 49 inches and weight 72 pounds. The gait is stiff but not waddling, and there is slight dorso-lumbar kyphosis together with genu valgum and infantile genitalia. The hands are broad with incurved fifth fingers, slightly cyanotic nail beds, and clubbed thumb nails. The fingers are flexed and the movement of the joints of both upper and lower limbs is restricted. The heart and lungs are normal but he is " losing power in his legs ", is very apprehensive, and has many periods of diurnal whining and crying as though he were suffering abdominal colic. During these phases he seeks comfort from his mother. The skin is normal. His bodily development is angular and, relatively, asthenic.

He is imbecile and his habits are becoming faulty. He could not cooperate in mental testing.

Case 3.—This is the first gargoyle (Fig. 2, II, 10) appearing in the pedigree and, according to his mother who died recently aged 90 years, he was the first case in the line of descent within her memory.

He died in a mental hospital aged 6 or 7 years. The records show that he was generally underdeveloped, with brown eyes and no abnormality in the corneae. He had a florid complexion, peg-like teeth, a tongue which tended to protrude, and a large umbilical hernia. He was unable to stand unsupported, made inarticulate noises, could do nothing for himself, and was faulty in his habits. He had no thumbs, except for a small, wart-like representation on the left hand. His weight was 39½ pounds and his stature small. Two sisters, aged 18 and 13 years respectively at the time of his death, describe him as having a " large, flat-looking face and a large stomach ". Their additional information corresponds with the medical description. No abnormality was noted in the skin.

His mental grade is given as idiot and the cause of death as pneumonia.

Case 4.—This child (Fig. 2, II, 13) died at the age of 7 years and was described by his sister, aged 20 years at the time of his death, as being " the same as his brother (Case 3) and his grand-nephew (Case 2) ". A photograph hung in the home for many years and the sister was, therefore, very sure of the likeness. He had a large, flat face, large head, clear corneae, a prominent abdomen with a hernia, could not walk unsupported, and had difficulty with his joints. His skin was normal.

His mental grade was imbecile. The cause of death is not known.

Case 5.—This boy (Fig. 2, III, 2) died aged 7 years and was described by his mother as being " like his brothers " (Cases 6 and 7). He had a large head, flat face and squat nose, clear corneae, stiff joints with flexed fingers, and a large abdomen, but no rupture. His skin was normal.

His mental grade was imbecile and the cause of death pneumonia.

Case 6.—This boy (Fig. 2, III, 5), who died at 11 years of age in a mental hospital, was also described by his mother as being like his brothers (Cases 5 and 7). In addition to the information given under Case 5 he had a large rupture from birth. He was markedly short of breath, so that he did not go out much. The corneae were clear. Thyroid treatment did not produce any improvement in his condition. His skin was normal.

His mental grade was imbecile and the cause of death unknown.

Case 7.—This boy (Fig. 2, III, 7 and Fig. 3) died at 12 years of age and was described by his mother as having a large, round head with coarse hair, flat nose, low-placed ears, short neck, hunched shoulders, knock knees, and stiff shoulder, elbow, and knee joints. He was small and he was late in walking and talking. Extensive thyroid treatment did not produce any improvement. He had a large abdomen but no rupture. His eyes were " beautiful " and his corneae clear. The skin showed no abnormality, and he was rotund in build.

FIG. 3

His mental grade was imbecile and the cause of death not known.

A photograph shows him to have been a gargoyle.

Case 8.—This child (Fig. 2, III, 8) died at the age of 5½ years in a, then, public assistance institution. Two aunts described him as being " the same as the others ". His mother stated that he had a large head, prominent eyebrows, coarse hair, squat nose, normal-sized tongue and that he was capable of saying a word or two and of running about. He had a marked " stoop across his back " and had difficulty in moving his fingers and elbows. His corneae were clear. He had a large abdomen but no rupture, and his skin was normal.

His mental grade was imbecile and he died during a fit.

A photograph taken at the age of 4 years was inspected and the diagnosis confirmed.

Case 9.—This boy (Fig. 2, III, 14), when he died aged 5 years 8 months, could just walk by helping himself along the wall. His mother says that he was very small, had a large head, early dental decay, could not speak and that his abdomen was protuberant with a fair-sized umbilical hernia. The tongue was not noticeably enlarged, his corneae were clear, and his eyelashes " long and beautiful ". He had difficulty in straightening his arms and fingers. When shown a photograph of his cousin (Case 7), the mother said, " he's just like my son ". His skin was normal. His mental grade was imbecile. The cause of death is not known.

Case 10.—This child (Fig. 2, III, 20), who died at the age of 10 years, was described by his mother. Pregnancy was normal but labour was difficult and instrumental and he was born " with the cord around his neck ". No abnormality was noted until he was 8 months old when his parents saw that his head was rather large and his general development slow. He did not walk until 2 years of age and only learned to say a few words during his lifetime. He had a large, globular head, with coarse hair and well marked eyebrows. There was infra-orbital puffiness and hypertelorism, but the corneae were clear. His ears were low placed, his nose squat and flat bridged, but his tongue was normal. The right shoulder was much higher than the left and both were hunched. His arms and fingers were stiff and he could not raise his hands above his head. The fingers were semi-flexed. He always had difficulty in lifting his legs and, towards the end of his life, could not walk properly. His abdomen was protuberant but there was no hernia. Thyroid treatment produced no improvement. His configuration was rotund and his skin normal.

His mental grade was imbecile, his habits were unclean, he never gained bladder control, and he was destructive to property. The cause of death was recorded as cerebral haemorrhage.

A photograph, reproduction of which was refused, shows him to have been a gargoyle.

Case 11.—This boy (Fig. 2, IV, 2 and Fig. 4) died on his birthday at the age of 14 years. His mother's health during pregnancy was good, the birth full term and labour both natural and rapid. No abnormality was noticed during the early weeks, but he did not teeth until he was

FIG. 4

nearly 2 years of age, nor walk until 3 years old. Speech was confined to a few simple words. He was described by his mother as having a largish head, with thick hair and bushy eyebrows. His nose was flat in appearance and his tongue rather large. He was subject to colds and bronchitis and was easily exhausted on walking. His corneae were clear. His neck was short, his shoulders hunched, his elbows flexed and his fingers markedly so. He had difficulty in abducting his arms and in extending his elbows and fingers. Genu valgum was present, he stood badly, and could not fully extend his knees. Thyroid treatment over a period of years produced no improvement. His configuration was, relatively, asthenic, and his skin normal.

His mental grade was imbecile and his habits faulty. The cause of death was pneumonia.

A photograph shows him to have been a gargoyle.

Case 12.—This boy (Fig. 2, IV, 6) died at the age of 9 years. Pregnancy, term, and labour were normal, and no defect was evident at birth. The onset of teething, walking, and talking were within normal limits, but bladder and bowel control were very late. His mother described him as having a large, round head, with coarse hair, bushy eyebrows, flat nose, and protruding lips. His tongue was large and his corneae clear, but his neck was short and his shoulders hunched. His elbows and fingers were partially flexed. He had difficulty in moving his fingers, and his legs appeared stiff with a clumsy gait. The abdomen was not noticeably enlarged.

Hospital records show that at the age of 7 years 4 months his height was 43 inches and his weight 53 pounds. There was an apical systolic murmur and he was bronchitic, suffering much dyspnoea. His teeth were poor and his speech defective. Administration of thyroid from an early age produced no improvement. No abnormality was noted in his skin.

His mental grade was imbecile and the cause of death pneumonia.

He was diagnosed a gargoyle by a neurological consultant. His younger, and only, brother, born after a difficult labour, won a scholarship to a grammar school.

Discussion

Examination of the pedigree (Fig. 2) shows that males are exclusively affected, in the ratio to normal brothers, of approximately one half, and that the parents are, in each case, normal. Maternal uncles are affected in a total of 10 cases and maternal grand-uncles in four cases. Cousin relationships exist in six and four cases respectively in two generations. These findings indicate that the mode of transmission in this family is through a sex-linked, recessive gene.

There are no first cousin relationships in any of the parents and more remote connexions are denied, although it is difficult to be sure of the accuracy of the latter information. It would seem reasonable to suggest, however, that the condition originated as a mutation in the first female (Fig. 2, I, 2).

Certain easily recognized clinical manifestations occur in the pedigree, among which may be mentioned the variation in bodily type, the clear corneae, the consistently low-grade defectiveness, and the absence of skin lesions. The combination of clear corneae and normal skin is of interest when one remembers that the corneal epithelium and the epidermis each develop from primitive ectoderm.

As the literature on gargoylism extends it is becoming clearer that the syndrome, at one time considered as rather a composite entity, is more accurately described as an assemblage of additive signs. Jervis (1950) indicates that one or more of the outstanding peculiarities may be absent and Jackson (1951) doubts whether the name is a good one, especially where the face is not affected. Although *formes frustes* undoubtedly occur, the description in the majority of cases is so apt that it seems inadvisable to rename the syndrome, at least until the exact nature of the tissue deposit is elucidated. Lindsay, Reilly, Gotham, and Skahen (1948) consider this to be a combination of glycogen and protein which is laid down in both an extra- and intra-cellular manner. Should this substance, indeed, prove to be non-lipoid in structure it would appear that gargoylism can no longer be pathologically classified with the lipoidoses of Gaucher, Niemann-Pick, Schüller-Christian, or Tay-Sach.

From the clinical standpoint it seems appropriate that the term " gargoyloid " be reserved for deviants from the main syndrome, and a diagnostic scale of any agreed degree of accuracy, based on a factorial analysis, set up. This would be comparable to what Penrose (1949) has suggested for mongolism. Cases 1 and 2 in the present series are contrasting physical types in so far as body outline is concerned, as were Cases 7 and 11. Such a diagnostic scale would not, of course, preclude the inclusion of gargoylism within the framework of the chondro-osseous dystrophies as a whole if, and when, a common genetic origin is revealed.

In diagnosis it is certain that Helmholz and Harrington (1931) erred in placing so much emphasis on the presence of cloudy infiltration of the corneae. On the other hand more research is required before one can assume with Njå (1945–46) that sex-linked inheritance is always accompanied by clear corneae, although Millman and Whittick's (1952) cases and the author's series are substantially indicative of this possibility.

All the cases in the present family are, and were, mental defectives and this is in accord with most of the literature on the subject. Jackson (1951), Gilliland (1952), and Straus, Merliss, and Reiser (1947), however, describe cases with normal, or near normal, intelligence. It is reasonable to assume that the degree of intellectual impairment is dependent upon the amount of infiltration of the cerebral tissues. Consequently, where feasible, an assessment of intelligence by standardized methods should always be carried out, as it would be of interest to correlate the impairment, as registered by mental age, with the degree and location of extra-cerebral pathology. In so doing the possibility of an independent amentia, due to other causes, would necessarily have to be borne in mind. This point may have been overlooked by Ashby, Stewart, and Watkin (1937) when these authors dissociated neuronic histochemical changes and intellectual retardation on the evidence obtained from the findings in one of their cases.

The average age at death in the present series is 8·7 years, and it would be valuable, with safeguards, to be able to compare the equivalent average morbidity in a group with higher intelligence.

Summary

A British family containing gargoyles in three generations, all of whom exhibited clear corneae, low-grade defectiveness, and normal skin, and in whom two main types of body structure could be detected, is described. The pedigree demonstrates the presence of a sex-linked, recessive gene.

The institution of a diagnostic scale, and the necessity for assessment of mental age in cooperative individuals, is commented upon.

I am grateful to Professor E. W. Anderson for advice and criticism in the production of this paper, to Miss Mansell of the Public Health Department, Essex County Council, for her invaluable assistance with the social studies, and to all the relatives, without whose patient cooperation progress would not have been possible.

References

Ashby, W. R., Stewart, R. M., and Watkin, J. H. (1937). *Brain*, **60**, 149.
Ellis, R. W. B., Sheldon, W., and Capon, N. B. (1936). *Quart. J. med.*, **29**, (n.s.5), 119.
Gilliland, I. C. (1952). *Proc. roy. Soc. Med.*, **45**, 594.
Halperin, S. L., and Curtis, G. M. (1942). *Amer. J. ment. Defic.*, **46**, 298.
Helmholz, H. F., and Harrington, E. R. (1931). *Amer. J. Dis. Child.*, **41**, 793.
Hunter, C. (1917). *Proc. roy. Soc. Med.*, **10**, (Sect. Study Dis. Child.), 104.
Hurler, G. (1919). *Z. Kinderheilk*, **24**, 220.
Jackson, W. P. U. (1951). *Arch. Dis. Childh.*, **26**, 549.
Jervis, G. A. (1950). *Arch. Neurol. Psychiat. Chicago*, **63**, 681.
Lindsay, S., Reilly, W. A., Gotham, T. J., and Skahen, R. (1948). *Amer. J. Dis. Child.*, **76**, 239.
Millman, C. G., and Whittick, J. W. (1952). *Journal of Neurology, Neurosurgery and Psychiatry*, **15**, 253.
Njå, A. (1945–46). *Acta paediat., Uppsala*, **33**, 267.
Penrose, L. S. (1949). *The Biology of Mental Defect*. Sidgwick and Jackson, London.
Straus, R., Merliss, R., and Reiser, R. (1947). *Amer. J. clin. Path.*, **17**, 671.
Wolff, D. (1942). *Laryngoscope, St Louis*, **52**, 218.

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A PERSISTING CHANGE IN PALMAR SWEATING FOLLOWING PREFRONTAL LEUCOTOMY

BY

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Le Gros Clark (1948) has suggested that the changes in the emotional life brought about by prefrontal leucotomy indicate that the frontal association areas may play an important part in the nervous regulations of autonomic function. As palmar sweating is under sympathetic control and is known to vary in a sensitive fashion with psychological stimuli, it seemed worthwhile to study the effect of leucotomy on resting palmar sweating and on the sudomotor reflexes.

Since the work of Kuno (1934) there has been an unfortunate tendency to regard palmar sweating as independent of thermo-regulatory requirements, and as purely emotional in origin. However, the earlier work of Richter (1929) suggests that palmar sweating is not independent of temperature regulation requirements. Our own preliminary observations confirmed that if the subject is appreciably off heat balance then thermo-regulatory requirements normally take precedence over psychic influences. Our doubts on this score have recently been amply confirmed by Conklin (1951) who showed that when other factors were controlled, palmar skin resistance varied inversely as the environmental temperature.

In order to form an estimate of the influence of thermo-regulatory requirements on palmar skin resistance, records were also kept of the mean environmental temperature, and of palmar skin temperature. Unfortunately, as explained below, skin temperature recordings were not made on all our subjects.

In addition to the influences of thermal and psychological factors, it is likely that palmar sweating is also related to muscular activity (Freeman and Simpson, 1938). This is a factor which in this series of observations it was not practicable to control. Although there is evidence that in this study this factor was not important, its possible influences must be kept in mind in interpreting our findings. Increases in environmental temperature and in muscular activity will tend to increase both palmar sweating and blood flow in the skin and thus, as skin temperature depends on blood flow, these factors will cause a positive correlation between sweat rate and skin temperature. Anxiety, on the other hand (except in so far as it increases metabolism), causes sweating and vasoconstriction. This variable will therefore cause a negative correlation between palmar sweating and skin temperature. Thus the correlation coefficient derived from concurrent observations on sweat rate and blood flow will vary between -1 and $+1$ depending on the respective contributions of these factors. That is to say, this value will increase positively as psychic factors are reduced in importance as a variable.

Methods

The palmar skin resistance was measured with an apparatus similar to that described by Grant (1946). Recordings of the psychogalvanic responses were made on photographic paper. The technique has been described and illustrated elsewhere (Elithorn, Piercy, and Crosskey, 1951). Palmar skin temperature was measured originally with a commercial "thermistor"; this was inadvertently broken by a patient and because of its long period of adaptation it was, after a delay, replaced by thermocouples and a galvanometer.

In the absence of a constant temperature room recordings were made at the temperature prevailing in the laboratory, which was also recorded. The subject rested in a sitting position with the arms supported comfortably at heart level. In addition to the records of laboratory temperature, we obtained figures for London temperatures as recorded at midday on the Air Ministry roof. Correlation coefficients were calculated for the initial skin resistance and London temperature and also for the final skin resistance and the laboratory temperature. Our subjects were present in the

laboratory for about half an hour. This time was not sufficient for them to establish a new thermoregulatory balance and the correlations presented are those for the initial readings and the London temperature.

In interpreting these correlation coefficients it must be remembered that during the immediately pre- and post-operative periods the patients were to some extent protected from the environmental temperature by the hospital. During the follow-up period they attended as out-patients. For some subjects, in addition to the observations on resting skin resistance, the psycho-galvanic responses to a sudden loud noise and to a maximal deep breath were also recorded. In others the responses to painful stimuli and the threat of painful stimuli were recorded. (The effect of leucotomy on these latter responses will be reported elsewhere.)

The number of patients available was small and the opportunities to study each one variable. Further, it was expected that they would show individual variations to a surgical procedure whose extent was always slightly doubtful. It was decided, therefore, to make as many serial observations on each patient as circumstances permitted. Relevant clinical details are mentioned in association with the individual findings. Full clinical details will be published elsewhere.

Results

Table I shows the means and the standard deviations calculated from the 298 occasions on which skin temperature and skin resistance were both recorded. These have been grouped into (1) pre-operative observations, (2) post-operative observations made in the first three post-operative months, and (3) follow-up observations made during the subsequent 21 months. A varying number of observations was made on 23 patients, and in order to avoid undue weighting by those patients on whom most observations were made, the overall means for each period have been calculated from the mean value for each patient for each period.

TABLE I

SKIN RESISTANCE, SKIN TEMPERATURE, AND LONDON TEMPERATURE

Period of Observation	Pre-operatively	First Three Months Post-operatively	After Third Month
Number of observations	94	140	64
Mean skin resistance in ohms $\times 10^3$	145 (S.D. = 45·9)	169 (S.D. = 38·2)	156 (S.D. = 56·2)
Mean skin temperature in °F.	81·7 (S.D. = 7·3)	85·5 (S.D. = 5·5)	87·4 (S.D. = 7·2)
Mean London temperature in °F.	53·8 (S.D. = 10·2)	55·3 (S.D. = 20·0)	59·5 (S.D. = 11·8)

Mean values obtained with 23 subjects.

It will be seen that for the period immediately following the operation there is a rise in the mean values for skin resistance (indicating a decrease in sweating), in skin temperature, and in the London temperature. In the follow-up period the mean value for skin resistance has fallen towards the pre-operative value, but the values for mean skin temperature and mean London temperature have risen further. Although the variability of these means as expressed by their standard deviations is high, Fisher's t test for the difference between means of paired observations shows that the changes in skin resistance and in skin temperature which follow the operation are both significant at the 5% level of confidence ($t = 2{\cdot}34$ and $2{\cdot}11$ respectively, $n = 22$). The increase in London temperature does not satisfy this test of statistical significance ($t = 1{\cdot}49 : 0{\cdot}1 < P < 0{\cdot}2$). However, by the follow-up period the mean environmental temperature has risen to 59·5° F., an increase of 5·7° F. over the mean temperature of the pre-operative period. This change in temperature satisfies the t test of significance ($t = 2{\cdot}46 : 0{\cdot}02 < P < 0{\cdot}05$). Although our observations were spread over two years it is clear that we must take into account a mean rise in environmental temperature which accompanies our post-operative observations. This is probably related to the known tendency for psychiatric patients to be at their worst in the late winter, and to the tendency of our medical and surgical colleagues to take their holidays in the summer months. As a consequence, the majority of our patients were operated on in the winter.

Tests of significance for the skin resistance and the skin temperature show that during the follow-up period the skin resistance is no longer significantly different from the pre-operative control findings ($t = 0{\cdot}90 : 0{\cdot}3 < P < 0{\cdot}4$). The change in skin temperature has, however, increased and has a higher level of confidence ($t = 3{\cdot}16 : 0{\cdot}01 < P < 0{\cdot}02$). Table II shows the correlations which have been derived from these observations. In all three periods the correlations of both palmar sweating and palmar temperature with the London temperature are positive. The correlation coefficient for palmar sweating and London temperature reaches a value which satisfies tests of significance only during the third or follow-up period. During the first two periods the patients were to some extent protected from environmental changes by their presence in

TABLE II

CORRELATION COEFFICIENTS BETWEEN SWEAT RATE (SKIN RESISTANCE), BLOOD FLOW (SKIN TEMPERATURE) AND LONDON TEMPERATURE FOR THE SAME PERIODS AS TABLE I

Period of Observation	Pre-operative	First Three Months Post operatively	After Third Post-operative Month
Number of observations	94	140	64
Sweat rate and London temperature	+0·140	+0·174	+0·321*
Blood flow and London temperature	+0·291*	+0·360***	+0·485***
Sweat rate and blood flow	+0·142	+0·327***	+0·276*

* Significant at 5% level of confidence.
*** „ „ 0·1% „ „ „

hospital. In spite of this the correlation of skin temperature with the external London temperature is significant in each period, and it is likely that heat elimination requirements play a dominant role in determining palmar skin temperature. It seems reasonable, therefore, to suggest that in the present series the skin temperature may be a more reliable indicator than London temperature of heat elimination requirements. Accepting this viewpoint for the moment, we may say that the post-operative increase in the correlation between the skin resistance and the skin temperature suggests that, after leucotomy, sweating is more closely related to thermo-regulatory requirements than to psychic factors. This dependence of sweating on thermo-regulatory requirements would appear to be most marked in the immediate post-operative period. Since the correlation coefficients show that in all periods skin temperature correlates positively with the environmental temperature, it is reasonable to conclude that the post-operative rise in mean skin temperatures shown in Table I may well depend very largely on the concomitant increases in environmental temperature. This change in temperature cannot account for the marked decrease in sweating (raised skin resistance) which occurs in the post-operative period. In fact, if psychological factors are held constant an increase in sweating must be expected in association with an increased environmental temperature. The further increase in temperature in the follow-up period could have contributed to the subsequent fall in the resistance towards the pre-operative value.

Adaptation Effects and Controls.—Unfortunately it was not possible to make similar serial observations on patients undergoing other intracranial operations. One patient undergoing a two-stage lumbar sympathectomy for hypertension was studied in detail. Following both operations she failed to show any marked rise in skin resistance and in fact showed a fall after each operation which may have been due to compensating sympathetic over-activity in the upper limbs. However, not all our patients had a full leucotomy, and it has proved possible to show clearly that the disturbance in palmar sweating is related to the extent of surgical intervention.

It has recently been confirmed by Conklin (1951) that skin resistance measurements show slight but definite adaptation when the observations are repeated on subsequent days. In order to exclude this as a possible cause of our findings we have analysed four seriatim observations, two immediately before and two immediately after the operation. The results are presented in Table III. They have been summarized separately for two groups of patients : first, 15 subjects who had a full standard leucotomy and, secondly, seven subjects who had minor surgical procedures—either unilateral leucotomies or bilateral operations of limited extent. One subject, who had only one pre-operative recording, has been omitted. In Table III those means, which are significantly different from

TABLE III

SERIATIM OBSERVATIONS ON RESTING SKIN RESISTANCE FOR 22 SUBJECTS

	Standard Leucotomy (N = 15)					Sub-standard Leucotomy (N = 7)				
	Session A	Session B		Session C	Session D	Session A	Session B		Session C	Session D
	Av. 6 days Pre-operatively	Av. 4 days Pre-operatively	OPERATION	Av. 7 days Post-operatively	Av. 11 days Post-operatively	Av. 6 days Pre-operatively	Av. 4 days Pre-operatively	OPERATION	Av. 7 days Post-operatively	Av. 11 days Post-operatively
Mean skin resistance in ohms × 10^3	154 (S.D. = 67·0)	142 (S.D. = 47·9)		213*** (S.D. = 68·0)	202 (S.D. = 77·6)	175 (S.D. = 70·1)	151 (S.D. = 41·9)		157 (S.D. = 50·8)	156 (S.D. = 45·9)
Mean London temperature in °F.	55·2 (S.D. = 6·5)	55·0 (S.D. = 9·5)		53·3 (S.D. = 11·2)	55·9 (S.D. = 9·5)	51·9 (S.D. = 6·3)	54·2 (S.D. = 8·9)		50·4 (S.D. = 9·4)	56·0 (S.D. = 12·7)

The asterisks show those figures which are significantly different from the preceding session at or above the 5% level of confidence.
*** denotes significant at 0·1% level of confidence.

the values found in the immediately preceding session, are indicated.

The only significant change between seriatim sessions occurs in the group undergoing full leucotomy. For this group Fisher's t test shows that the differences between the means for the two pre-operative sessions are not significant. The mean skin resistances for the two post-operative sessions are both significantly higher (at the 1·0% level of confidence) than those in either pre-operative session. Further, the difference between the means of the two post-operative sessions is not significant. In the group of seven patients who had restricted operations, none of the changes between sessions is significant. Of these seven patients, only four showed a rise in skin resistance between sessions B and C, i.e., between the immediately pre-operative and the immediately post-operative session. Of the 15 patients receiving a full leucotomy only one failed to show such a rise.

Although the number of subjects is small, it is possible to show by means of a contingency table that environmental temperatures play a role in determining individual changes from session to session. Such a presentation has the advantage of demonstrating more directly the irrelevance of environmental temperature variations to the marked decrease in palmar sweating brought about by leucotomy. Table IV shows (1) the contingency of changes in skin resistance between sessions A and B on changes in London temperature and (2) the contingency of changes in skin resistance between sessions B and C on changes in London temperature. It can be seen that in the case of the two pre-operative sessions this contingency is marked but in the case of the two sessions separated by the operation the rise in skin resistance is independent of changes in London temperature. Any surgical operation is sometimes followed by a period of impaired temperature regulation with pyrexia. The ward records of axillary temperature showed such a disturbance for most of our subjects but this lasted only a few days. Observations on the oral temperatures of 12 of our subjects confirmed that our results could not be explained as a failure of temperature regulation, the mean value for 52 observations of a three-minute oral temperature pre-operatively being 98·2° F. (S.D. = 0·66). For 64 observations made in the first three months post-operatively the mean value was 98·3° F. (S.D. = 0·68). These means are not significantly different.

TABLE IV

RELATIONSHIP BETWEEN CHANGES IN SKIN RESISTANCE AND CHANGES IN LONDON TEMPERATURE FOR 22 SUBJECTS

	Rise in Skin Resistance	Fall in Skin Resistance
1. *Changes between Session A and Session B.*		
Rise in London temperature ..	3	7
Fall in London temperature ..	7	5
2. *Changes between Session B and Session C.*		
Rise in London temperature ..	9	1
Fall in London temperature ..	9	3

Follow-up Studies.—The overall means presented in Table I suggested that the effect of leucotomy on the skin resistance persisted for at least three months, though this observation did not reach a significant level of confidence. The mean value for the skin resistance during the follow-up period included however the observations made on subjects who had had only partial leucotomies. Further, most of the recordings were made on days with a relatively high environmental temperature. In order to throw further light on this point we have undertaken a separate analysis of our follow-up observations on those subjects who had a full leucotomy and were examined at least six months after operation. Twelve subjects came into this category and for these 12 subjects we have analysed the observations made at their most recent visit, thus ensuring the maximum possible lapse of time between the operation and follow-up observation. The mean follow-up period is two years, the actual values in months for the 12 subjects being 6, *11*, 11, *13*, *18*, 18, *27*, *32*, *35*, 38, *39*, and 43. Of these 12 subjects, the seven whose follow-up time is presented in italics showed skin resistance levels higher than both the values recorded in session A or session B. The mean values for this group are given in Table V, where this follow-up session is designated F. The mean skin resistance value for this session is higher than those recorded pre-operatively. The difference between session F and session B is significant at the 1% confidence level, but the difference between session F and session A does not reach a significant (5%) level of confidence. This difference cannot be accounted for by environmental changes, the mean temperature being slightly higher for the follow-up observations than for either of the pre-operative sessions.

Thus we can conclude that in this group of cases, a standard prefrontal leucotomy caused a marked decrease in palmar sweating which persisted well beyond the immediate post-operative period, and further that this is not due to a failure of the temperature-regulating mechanism. Control observations

TABLE V

FOLLOW-UP STUDIES OF 12 LEUCOTOMY PATIENTS

	Session A	Session B	OPERATION	Session C	Session D	Follow-up Session F
Mean levels of skin resistance in ohms × 10^3	151 (S.D.=74·8)	143** (S.D.=65·1)		203 (S.D.=63·8)	196 (S.D.=64·4)	180 (S.D.=65·5)
Mean London temperature in °F.	55·1 (S.D.=7·0)	55·0 (S.D.=10·6)		54·7 (S.D.=11·6)	57·0 (S.D.=9·7)	55·9 (S.D.=13·1)
Mean days to operation	−6	−4		+8	+10	+764

The asterisks show those figures which are significantly different from those found at follow-up session F.

** Significant at 1% level of confidence.

show that it is related to the extent of tissue damaged and is not caused by the anaesthetic or surgical operation *per se*. The material is not adequate to indicate whether the site of the lesion is important.

Individual Results.—We have argued elsewhere (Elithorn and others, 1954) that the effect on autonomic functions of surgical trauma to the frontal lobes will vary in individual subjects and will in the case of psychiatric patients depend to a large extent on the nature of the pre-operative morbid state. Most workers interested in skin resistance agree with Richter (1928, 1929) that the palmar resistance tends to be high in depressive illnesses and is low in conditions associated with anxiety. Unfortunately almost all our subjects were both depressed and anxious; not one was severely retarded. It is interesting to note, however, that the patient who showed the highest pre-operative skin resistance was subject J.G. who was the only patient suffering from a recurrent endogenous depression.

Fig. 1 shows graphically the types of change which were observed in individual patients.

Patient F. C. (Hospital No. 11564).—This patient, a woman aged 41 (Fig. 1, 1), shows the effect of the standard operation on the skin resistance of a patient of life-long anxious and hypochondriacal personality, who at the age of 38 developed an agitated depressive illness. Leucotomy produced a complete remission. Personality changes were mild and beneficial in that she was no longer abnormally over-anxious, but showed no unequivocal changes for the worse. With this patient the change in skin resistance was not marked. The post-operative values are well within normal limits but equally are consistently higher than those recorded pre-operatively.

Patient N. P. (Hospital No. 11405).—This patient, a woman aged 43, suffered from a chronic anxiety state with a morbid preoccupation with her total alopecia, and a constant fear that her wig would be detected, Following standard leucotomy there was a definite reduction in her tension, though the recurrence of her fears led eventually to a second operation. Following a prolonged period of rehabilitation she made a good recovery. Fig. 1, 2 shows that after her first operation there was a marked increase in skin resistance.

Patient E. C. (Hospital No. 12233).—Fig. 1, 3 shows the effect of a standard leucotomy on a patient who suffered from a chronic paranoid schizophrenic illness of at least 10 years' duration. The operation produced no alteration in the essential illness but a definite temporary reduction in tension. After leucotomy there was a marked temporary elevation of the skin resistance.

Patient J. G. (Hospital No. 13310).—This lady, aged 66 years, was suffering from her second attack of endogenous depression, an illness of three years' duration, in her instance attended by considerable fear, anxiety, and somatic sensations. There was no pathological guilt or delusions or hallucinations. Retardation was not marked. A standard leucotomy produced a complete remission of her illness and a definite frontal lobe syndrome. The resting skin resistance readings (Fig. 1, 4) obtained from this patient were quite low at first, but rose quickly to an abnormally high level as she became accustomed to the test procedure; her contact with the environment and her marked tendency to react with anxiety are well demonstrated by the low level recorded at the first session and the sudden drop in resistance which accompanied her transfer to the surgical ward. After leucotomy she showed the usual post-operative high levels of palmar skin resistance although in fact these are less high than those associated with her depressive illness

Patient E. M. (Hospital No. 8663).—This patient, a woman aged 53, suffered from an involution hypochondriasis which centred around abnormal throbbing sensations within her belly. Rostral leucotomy produced a very slight and transient improvement. A standard leucotomy a year later again failed to alter her main symptoms but there was undoubtedly a great reduction in the anxiety and depression associated with her illness. Fig. 1, 5 shows that following the minor rostral operation there was no marked effect on the palmar sweating. Following the standard operation the skin resistance showed a very definite rise similar to that found with most patients who had had standard leucotomies.

Psychogalvanic Responses.—The psychogalvanic responses which were recorded to a sudden loud noise and to maximal inspiration showed great variability both as between different subjects and as

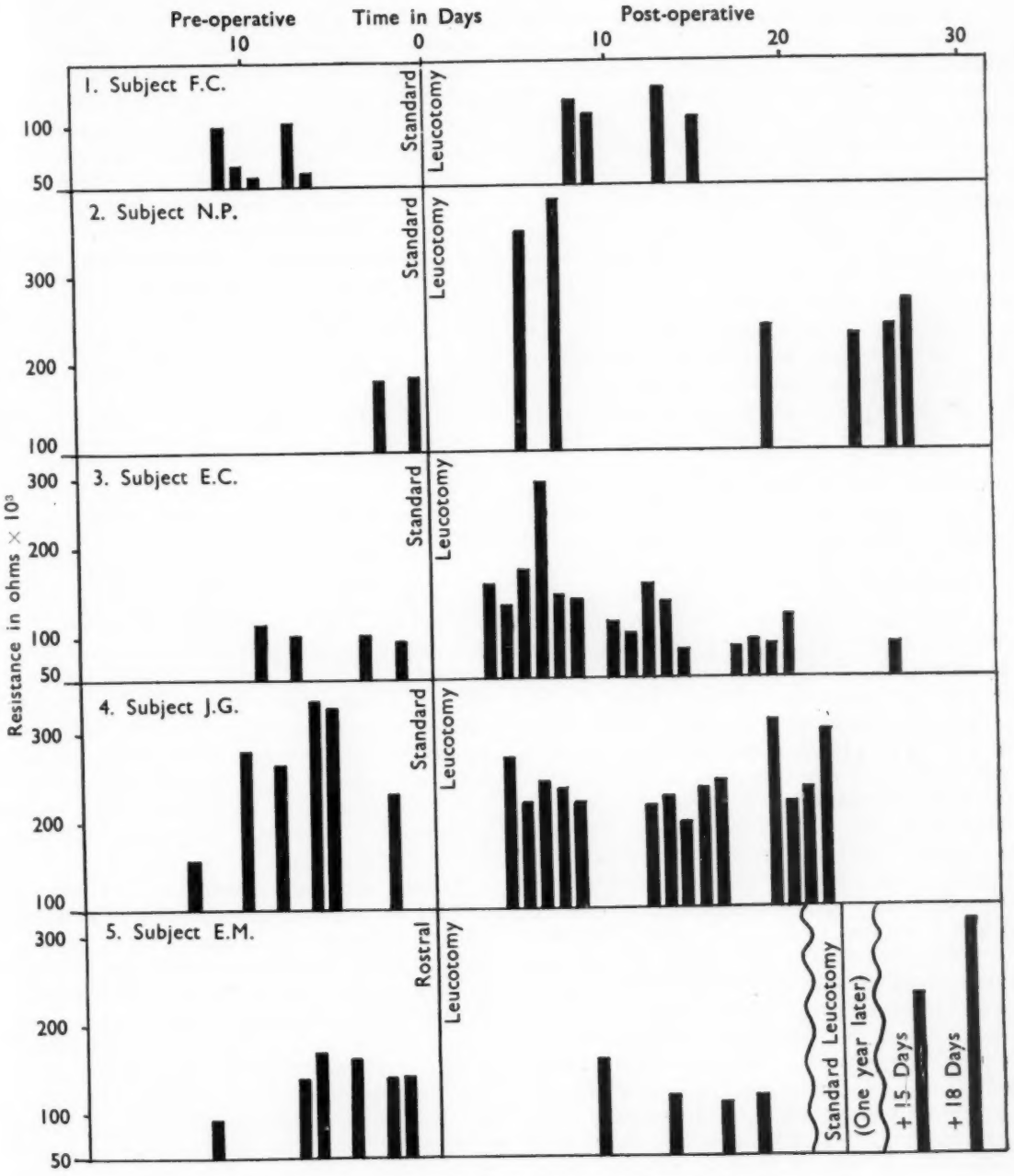

FIG. 1.—Changes in resting skin resistance following prefrontal leucotomy.

between different occasions for the same subject. There was definite adaptation of the responses with repetition of the stimulus—especially the startle noise. For the group as a whole the gradual decrease in size of responses from session to session was temporarily interrupted by leucotomy. The effect did not satisfy tests of significance and inspection of the individual results suggested that individual subjects responded in opposite ways to leucotomy. In those in whom anxiety was the prominent pre-operative symptom leucotomy tended to produce a marked reduction in the responses. Where depression was predominant the responses were for a short time post-operatively much exaggerated in size, but quickly adapted with repetitions. Although these results are not presented in detail and were not suitable for statistical analysis they are mentioned here because they confirm Ashby and Bassett's tentative conclusions. The results obtained with other stimuli will be reported in detail elsewhere.

Discussion

A paper by Ashby and Bassett (1950) is, as far as the present authors are aware, the only report of an investigation primarily undertaken to study the effect of leucotomy on palmar sweating. Several other authors have used various estimations of palmar sweat function amongst other " indices " of " autonomic reactivity ". Thus, Malmo and Shagass (1950) state that following lobotomy patients show larger psychogalvanic responses to painful stimuli. The Columbia-Greystone Associates (1949, 1952) report that various forms of psychosurgery cause an increase in the fall in palmar skin resistance which follows the intravenous injection of " methacholine ". Unfortunately these authors do not give the initial levels of skin resistance though they mention in passing that these were very high post-operatively in the two patients who underwent cortical thermocoagulation. Glaser (1952) in an interesting study has considered carefully the effect of the pre-operative mental state of his subjects. He compares the effects of two types of frontal topectomy (dorsal and orbital) on the autonomic stability of two groups of schizophrenics. Both paranoid schizophrenics and hebephrenic-catatonic schizophrenics showed an increase in resting skin resistance and a greater reactivity to intravenous " mecholyl ", regardless of which type of operation was performed. With the cold pressor test, the paranoid group showed a reduction in reactivity, while the hebephrenic-catatonic group, which before operation had been hyporeactive, showed increased reactivity.

Ashby and Bassett (1950) examined only the reflex activity of the skin resistance. They compared the psychogalvanic responses to eight startle stimuli in two matched groups, each of 21 patients with varied symptoms. The group which had previously been subjected to leucotomy was significantly less reactive than the control patients. In a smaller but more precise study reported at the same time, they examined six subjects on three occasions before and on three occasions after the operation. Some of these subjects showed increased responses following leucotomy and some decreased responses. This effect they found to be significant at the 1% level of confidence. Ashby and Bassett examined patients subjected to both standard leucotomy and orbital " ice pick " leucotomy. They do not report any difference in results between subjects undergoing these two types of operation, nor do they say in what particular the effect of the operation depended on the pre-operative clinical picture.

Mettler and Landis (1952) writing the concluding chapter to the second of the Columbia-Greystone studies say :

> " The present data tend to confirm the general findings of the previous project in which it was pointed out that the physiological effects of granular frontal cortical removal were qualitatively and quantitatively less extensive than the literature would lead one to suppose."

Unfortunately the Columbia-Greystone project, which is clearly the most detailed and comprehensive physiological investigation to date on the effects of various psychosurgical procedures, was undertaken on deteriorated schizophrenics. Our own analysis of the literature which is given above and which is here confined to those papers dealing with the effect of leucotomy on palmar skin resistance, combined with our own observations, supports the following conclusions.

Palmar sweating in mental disease may be increased in association with subjective feelings of anxiety, agitation or distress. In so far as these symptoms are relieved by leucotomy, there is likely to be a concomitant decrease in palmar sweating. In depressive illnesses—especially those of the endogenous type associated with retardation and poverty of thought—there is said to be (Richter 1928) a relative failure of palmar sweating and a decrease in the psychogalvanic responses to many types of stimuli. (Our present experience is limited to one case.) Following a successful leucotomy (as in fact happens in our one case) palmar sweating is likely to increase and responsiveness to return. In the present series, with one exception (a hypertensive patient who showed clinical evidence of a posterior and severe leucotomy and for a few days post-operatively suffered from syncopal attacks) we have

not found any evidence of failure of homeostatic physiological mechanisms. Indeed, the positive correlation between sweat rate and skin temperature was higher in the immediate post-operative period than either before operation or during the follow-up period. Carscallen, Buck, and Hobbs (1951) have shown that after leucotomy schizophrenics show improved temperature regulation. These findings also are in line with Reitman's (1945) conclusions that with schizophrenic patients after standard leucotomy there is a tendency towards increased rather than decreased "homeostasis". We would add that leucotomy also reduces the abnormal autonomic activity associated with the mental disease.

Summary

Studies on palmar skin resistance (palmar sweating) have been carried out on 16 patients undergoing bilateral standard leucotomy, four undergoing unilateral leucotomy, and three undergoing rostral cortical undercutting.

A group of 12 patients subjected to standard leucotomy showed post-operatively a significant increase in skin resistance which was present, though to a diminished extent, more than six months after leucotomy (mean follow-up time two years). This effect was not detected in the group of seven patients undergoing minor psychosurgical procedures.

Individual studies showed that the alterations in skin resistance which followed prefrontal leucotomy were related to the changes which occurred in the mental state. They were not related to changes in thermo-regulation.

The literature on the effects of prefrontal leucotomy on palmar skin resistance is reviewed.

Our thanks are due to the physicians and surgeons of the National Hospital who allowed us to study patients under their care, to Dr. Eliot Slater, under whose care most of these patients were, and who saw the remainder in consultation, we are particularly indebted for an authoritative opinion on their psychiatric state. To Dr. Carmichael and Professor Zangwill we are grateful for advice, criticism, and material help.

References

Ashby, W. R., and Bassett, M. (1950). *J. ment. Sci.*, **96**, 458.
Carscallen, H. B., Buck, C. W., and Hobbs, G. E. (1951). *Arch. Neurol. Psychiat., Chicago*, **65**, 206.
Clark, W. E. Le Gros (1948). *Lancet*, **1**, 353.
Conklin, J. E. (1951). *Amer. J. Physiol.*, **64**, 78.
Columbia-Greystone Associates (1949). *Selective Partial Ablation of the Frontal Cortex*, ed. Mettler, F. A. Hoeber, New York.
——(1952). *Psychosurgical Problems*, ed. Mettler, F. A. Routledge and Kegan Paul, London.
Elithorn, A., Piercy, M. F., and Crosskey, M.A. (1951). *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 209.
——, ——, ——(1954). *Ibid.*, **17**, 139.
Freeman, G. L., and Simpson, R. M. (1938). *J. gen. Psychol.*, **18**, 319.
Glaser, G. H. (1952). *J. nerv. ment. Dis.*, **115**, 189.
Grant, D. A. (1946). *Amer. J. Psychol.*, **59**, 149.
Kuno, Y. (1934). *The Physiology of Human Perspiration*. Churchill, London.
Malmo, R. B., and Shagass, C. (1950). *Arch. Neurol. Psychiat., Chicago*, **63**, 113.
Mettler, F. A., and Landis, C. (1952). In *Psychosurgical Problems*, p. 313. London.
Reitman, F. (1945). *J. ment. Sci.*, **91**, 318.
Richter, C. P. (1928). *Arch. Neurol. Psychiat., Chicago*, **19**, 488.
——(1929). *Amer. J. Physiol.*, **88**, 596.

J. Neurol. Neurosurg. Psychiat., 1954, **17**, 204.

THE EFFECT OF CARDIAZOL CONVULSIONS ON THE DISTRIBUTION AND ACTIVITY OF SOME PHOSPHATASES IN THE AREA POSTREMA OF THE RAT

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During previous studies on the localization of phosphatases in the central nervous system of the rat it was observed that the area postrema showed intense enzyme activity to a number of important phosphoric acid esters in the acid and alkaline ranges. This structure therefore provided a convenient point upon which to test the effects *in situ* on some brain enzymes of substances used in neuropsychiatric therapy.

Since anatomical information on the area postrema of the rat was limited, a preparatory study of the medulla was undertaken to establish the normal histology. Cardiazol was the test substance of choice because accurate doses could be administered intravenously and because the subsequent convulsions could be assessed readily according to length and severity.

Material and Methods

Preparatory anatomical and histological work was carried out on 22 adult albino rats weighing between 200 and 250 g. The methods applied were the ordinary histological staining procedures including various silver impregnation techniques.

A histochemical study of the area postrema was made on the frozen-dried brains of 45 adult albino rats. The femoral veins of anaesthetized rats were exposed and 0·05 g. of "cardiazol" in a 10% solution in double-distilled water was injected. The convulsions began immediately and the animal was transferred to a chamber into which a small constant flow of oxygen was directed to avoid anoxia. The rats were in convulsions between a half and four hours. Control animals were injected with an equal volume of distilled water and placed in the same atmosphere. An experimental animal and its control were anaesthetized together and both brains were removed rapidly. The cerebellum was then cut through approximately between its anterior two-thirds and posterior third. The caudal block containing the area postrema was immediately dropped into isopentane cooled to below −65° C. in a bath of acetone and CO_2 ice.

After about two to five minutes the material was transferred to a drying tube made of pyrex glass 15 cm. × 3 cm. provided with a B34 ground socket. The tube was previously filled to the level of about 2.5 cm. with paraffin wax (m.p. 52° C.) and cooled to −78° C. in the acetone and CO_2 ice bath. The material was placed on this wax bed. The tube was then affixed to the vacuum pump (2.S.50 Edwards) by means of a glass wide-bore adaptor. Between adaptor and pump was interposed an isolation valve and a P_2O_5 trap. The tube was then surrounded by a bath (a 2-litre Dewar flask) of phenyl-ethyl-ether cooled to about −75° C. with CO_2 ice. The pump was started and the process of dehydration began. The phenyl-ethyl-ether bath was allowed to rise to about −30° C. at which temperature it was maintained by the addition of CO_2 ice. The pressure was frequently measured by a hot-wire Pirani gauge incorporated with the adaptor connecting tissue tube to the vacuum pump. The working pressure was about 0·02 to 0·002 mm. Hg and the time required for adequate drying was about 72 hours. When this period of time had elapsed the temperature was allowed to rise to room temperature by removal of the refrigerant. After 30 minutes at room temperature the pressure in the tube containing tissue was brought up to between 2 and 10 mm. Hg by the introduction of dry air. Having done this, the paraffin bed in the tube was slowly melted by surrounding the tube with a warm water bath. In this manner vacuum embedding in dry air was obtained. The temperature of the wax was not allowed to rise beyond about 56° C. After wax penetration for 20 minutes the tube was removed and the blocks embedded in paraffin of the same melting point as that which made up the wax bed. These blocks were stored at 0° C. in a dessicator. The tissue blocks were cut within one month of embedding. Sections 15 μ thick were mounted on albuminized 3 × 1 in. slides without floating on water. The sections were placed in a 37° C. incubator for 60 minutes. De-waxing was carried out by successive immersions for less than two minutes altogether in light petroleum (b.p. 100 to 120°), petroleum (b.p. 60 to 80°), and isopentane (b.p. 27 to 31° C.). The last solvent evaporated immediately after the section was removed from the de-waxing jar. The sections were placed at once in the prepared sub-

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strate media contained in coplin jars. The media were made up as the following formulae indicate.

Adenosine Triphosphate pH 6·5	
0·002 M stock solution ATP	7·5 ml.
0·1 M sodium succinate buffer	15·0 ml.
0·04 M lead acetate (neutral)	0·75 ml.
Glass-distilled water to	30·0 ml.
Adenosine Monophosphate pH 6·5	
0·1 M sodium succinate buffer	15·0 ml.
0·04 M lead acetate	1·5 ml.
0·01 M adenosine monophosphate	3·0 ml.
Glass-distilled water to	30·0 ml.
Aneurin Pyrophosphate pH 6·9	
0·1 M sodium maleate buffer	15·0 ml.
0·005 M aneurin pyrophosphate	3·0 ml.
0·1 M magnesium chloride	6·0 ml.
0·04 M lead acetate	0·75 ml.
Glass-distilled water to	30·0 ml.
Glycerophosphate pH 5·3	
0·1 M sodium acetate buffer	15·0 ml.
0·04 M lead acetate (neutral)	1·5 ml.
0·1 M stock solution glycerophosphate	3·0 ml.
0·1 M magnesium chloride	1·0 ml.
Glass-distilled water to	30·0 ml.
Glycerophosphate pH 9·1	
0·1 M sodium barbiturate buffer	7·5 ml.
1·0 M calcium chloride	3·0 ml.
0·1 M sodium glycerophosphate	6·0 ml.
Glass-distilled water to	30·0 ml.
Aneurin Pyrophosphate pH 9·1	
0·1 M sodium barbiturate buffer	7·5 ml.
1·0 M calcium chloride	3·0 ml.
0·005 M aneurin pyrophosphate	6·0 ml.
Glass-distilled water to	30·0 ml.

The preparation of adenosine triphosphate, adenosine monophosphate, and of the buffer solutions followed the methods advised by Naidoo and Pratt (1951 and 1952a or b).

The substrate medium was degassed immediately before the introduction of the sections. In order to ensure further that no gas bubbles would adhere to the surface of the tissue the slides were flicked into the medium with a sharp movement of the fingers so that they went in very rapidly. Incubation proceeded for intervals of 3, 10, 20, 40, 80, and 120 minutes. The sections were then removed, washed in four changes of ice-cold, glass-distilled water, and then placed for two minutes in 2% $(NH_4)_2S$ solution.

A comparison between the experimental and control series was made by cutting ribbons of sections on a rotatory microtome from single blocks of each series, and one anatomically similar section each from two comparable ribbons from separate blocks were incubated together on the same slide at the same level on the slide. Three separate criteria were employed in assessing histological enzymatic activity. First, a histological comparison of both sections incubated for the same time, secondly the difference in incubation time required to produce an equal depth of staining (Naidoo and Pratt, 1953), and thirdly a comparison of the response to inhibitors used with the normal control and the experimental material (Naidoo and Pratt, 1953).

Results

Anatomical and Histological.—The ependymal conus (area postrema) of the rat starts caudally at a point some 650 μ below its cephalic margin at the midpoint of the dorsal median raphe behind the commisural nucleus of Cajal. Vessels from the posterior median fissure are directed towards this site which is made up of mesodermal and glial fibres. About 150 μ rostral to this point the conus is larger, round, and its ventral limits are clearly demarcated by a dense glial wall whereas laterally the borders are indistinct. Further forward the absence of a definite lateral boundary gives the impression that the structure of the conus becomes intimately associated with that of the nucleus solitarius. At this point the central canal becomes T-shaped in cross section and the conus more wedge-shaped. There is a thick glial fibre bundle connecting the central part of the ventral surface of the conus to the central canal. In between these fibres there are some astrocytes and ependymal cells. As the restiform bodies diverge and the fasciculus solitarius with them, the conus is stretched out into a fan-shaped structure whose handle lies in the roof of the central canal. Further cephalad the stretched conus forms the roof of the central canal but the anterior boundary is reached soon after the conus becomes an intraventricular structure. At each lateral end of the anterior boundary, which may be visualized as the base of a triangle, a short, thick prolongation of the conus is seen.

The conus, then, is dorsally related to the central canal and connected to its ependymal lining by a ventral glio-ependymal prolongation from it ; it is related, by making contact with it, to the nucleus solitarius by a prolongation running laterally below the posterior funiculi of the medulla. The nucleus solitarius lies between this prolongation and the dorsal nucleus of the vagus. The intermediate zone between the pars magnocellularis of the nucleus solitarius and the ventrolateral border of the ependymal conus is occupied by what has been called the subnucleus tracti solitarii parvo cellularis by Meesen and Olszewski (1949).

The boundaries of the conus are definite except antero-laterally and at the ventral midpoint where prolongations exist. It is a highly vascular and cellular area. The vascular arrangement is that of a sinusoidal bed in which are set, among the sinusoids, astroglia, microglia, fibroblasts, and a type of cell containing a large oval clear nucleus with often an eccentric nucleolus and a small amount of chromatin. The larger of the cells lie at the periphery. Bielschowsky's silver technique reveals a very small number of protoplasmic processes. The astrocytic processes are not traceable readily to the walls of the sinusoids. Large amounts of collagen are seen around the vessels and the glial wall delimiting the conus is seen to be built up by processes of fibrous astroglia. Extensive search after the use of various silver techniques failed to demonstrate any structure

FIG. 1

FIG. 4

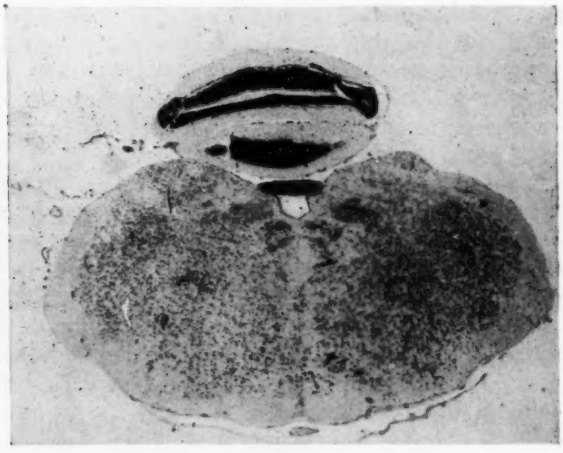

FIG. 2

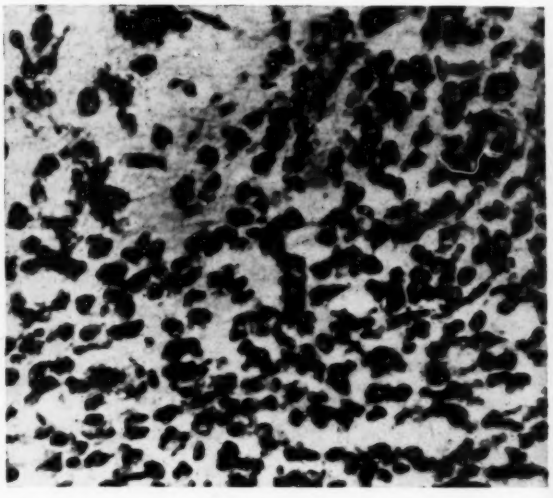

FIG. 5

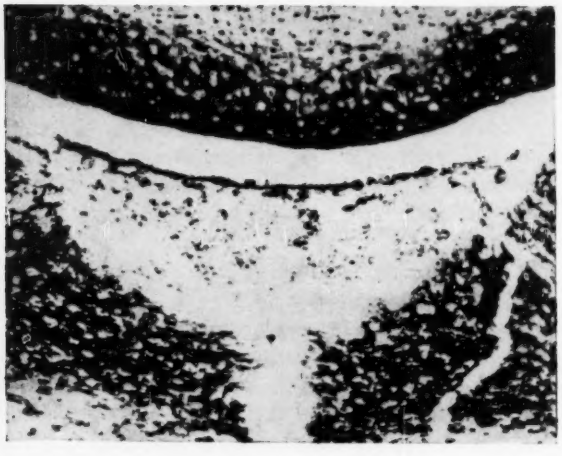

FIG. 3

FIG. 1.—Area postrema showing relation to medullary structures. × 26. Heidenhain stain.

FIG. 2.—Anterior end of area postrema showing bridge over central canal at apex of the fourth ventricle. × 14. Nissl stain.

FIG. 3.—Adenosine-monophosphatase *p*H 6·5 : relatively no activity. × 90.

FIG. 4.—Glycerophosphatase *p*H 9·1 : intense activity of area postrema. × 12.

FIG. 5.—Aneurinpyrophosphatase *p*H 6·9 showing strong activity in parenchymal cells. × 350.

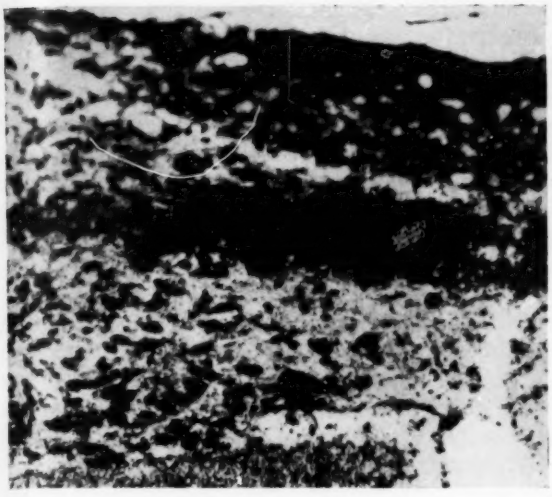

FIG. 6

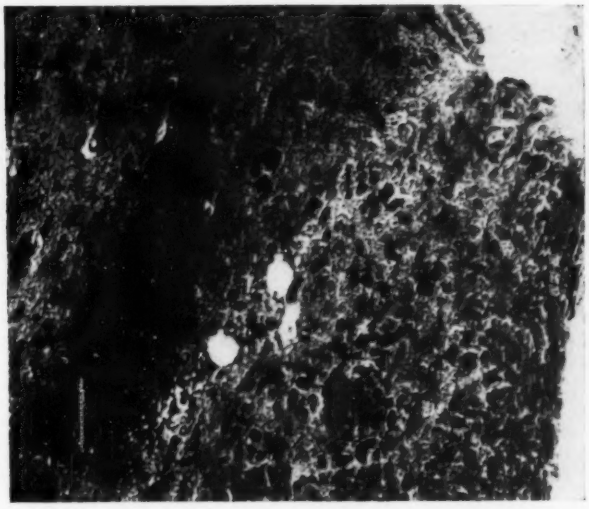

FIG. 8

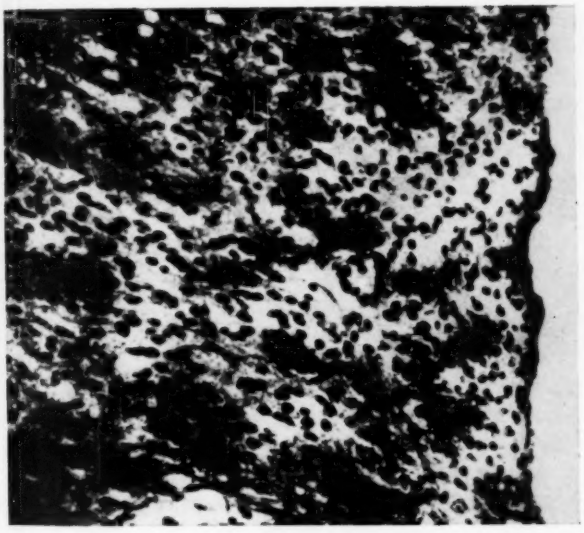

FIG. 7

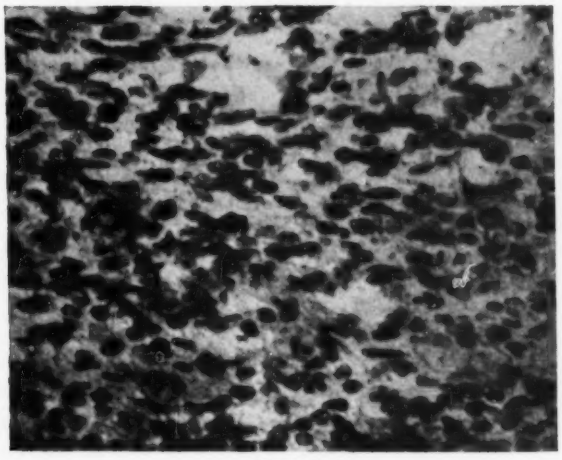

FIG. 9

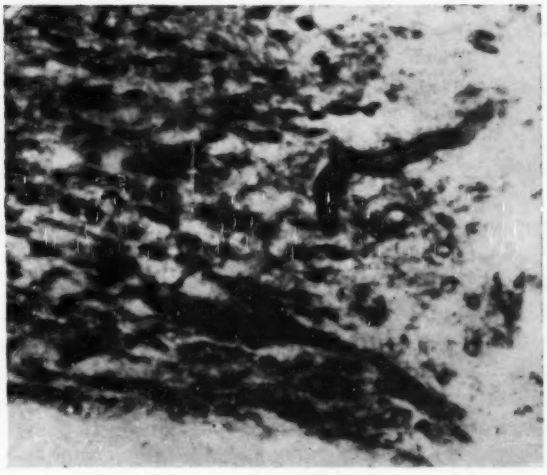

FIG. 10

FIG. 6.—Glycerophosphatase *p*H 5·3 showing strongly active area postrema and intense activity in the intermediate zone. × 140.

FIG. 7.—Adenosinetriphosphatase *p*H 6·5 : intense activity of nuclei of all cells and of nuclei of capillary cells. × 125.

FIG. 8.—Glycerophosphatase *p*H 5·3 (after cardiazol convulsions) : activity much reduced. × 160.

FIG. 9.—Aneurinpyrophosphatase *p*H 6·9 (after cardiazol convulsions) : activity much reduced. × 350.

FIG. 10.—Aneurinpyrophosphatase *p*H 9·1 (after cardiazol convulsions) : activity increased, activity in capillaries greatly increased × 320.

which could be indubitably described as an axon. Reticulin methods show abundant reticular fibres around the sinusoids and a thick layer in the outer surface of the conus. The larger cells with oval nuclei, which form the main cell of the parenchyma of the area postrema, appear to be modified ependymal cells.

Adenosine-monophosphatase : Normal.—The hydrolysis of adenosine monophosphate is found to be situated in the fibres of the medulla but by sharp contrast the area postrema stands out as a clear, unstained triangular area (Fig. 3). The outer border of the conus, however, appears a little more deeply stained than the remaining fibres of the medulla. Within the conus itself it is difficult to discern any staining of separate cellular elements. Here and there a short, thin fibre can be seen to be stained. At the longer incubation periods the cells, particularly those described above as parenchymal cells, begin to show slight staining. Nucleolar staining is inconsistent and appeared only in a few cells. The main impression is the absence of hydrolytic activity to adenosine monophosphate in the area postrema.

Adenosine-monophosphatase after Cardiazol.—The histochemical observations on the area postrema of animals convulsed with "cardiazol" show that the sites of hydrolysis of adenosine monophosphate in the area postrema are unaltered after convulsions. The area remains clearly demarcated as an unstained wedge. The rate of staining in the fibres of the medulla shows no change.

Glycerophosphatase *p*H 9·1 and 5·3 : Normal.—When sections which have been incubated with glycerophosphate at *p*H 9·1 are examined, the conus appears after 40 minutes' incubation as a black triangle set in a grey mottled background of medulla (Fig. 4). The conus thus shows intense enzyme activity with this substrate. The activity is so great that a positive result was obtained after an incubation period of two minutes. At such short incubation periods activity of the capillary endothelium can be distinctly demonstrated. Longer incubation periods increase the staining of the capillaries and the intersinusoidal parenchyma also begins to turn grey. The greyness does not start in the cells or collagen but is general and evenly distributed over the whole area. The area postrema and the choroid plexuses are the parts of the brain which stain most deeply after incubation with glycerophosphate at *p*H 9·1. At *p*H 5·3, however, the localization of the sites of enzyme activity differ from those found in the alkaline *p*H. In the area postrema the parenchymal cells are stained but not the sinusoids or glial cells. The parenchymal cells themselves appear to vary in their reaction to glycerophosphate. Some stain much more deeply than others over the same incubation period. That segment of tissue described as the intermediate zone (subnucleus tracti solitarii parvo-cellularis) between the conus on the one hand and the vagal and hypoglossal nuclei on the other, also shows strong enzyme activity (Fig. 6). The nuclei of the vagus and hypoglossal nerves show neuronal staining and in the longer incubation periods some parenchymal staining as well. The neurons show deep cytoplasmic staining, a clear nucleus, and a stained nucleolus. At the level of the fibroglial boundary there is a clear demarcation between the homogeneously stained intermediate zone and the conus in which only the parenchymal cells are stained.

Glycerophosphatase after Cardiazol.—In the sections incubated in glycerophosphate at *p*H 9·1 the reaction in the tissue from convulsed animals is considerably accelerated. After an incubation period of two minutes the capillaries in the experimental tissue are much darker than those of the control tissue. The whole area also appears darker : no definite cytological elements can be seen in the intercapillary spaces but the parenchyma generally takes part in the increased rate of staining. Even against this darker background the staining of the capillary walls is proportionately greater. After long incubation periods of one hour or more the differences become less discernible and by 90 minutes both normal and experimental areae postremae are equally black. At *p*H 5.3 the area postrema of the experimental animal stains considerably less than that of the control. In those animals in which convulsions were of relatively short duration—about half-an-hour—before the removal of the brain, the intermediate zone (subnucleus tracti solitarii pars parvocellularis) stains deeply but when the convulsions are prolonged up to about four hours the intermediate zone as well as the conus fails to stain. The longer the animal remains in a state of convulsion the more slowly does the intermediate zone hydrolyse glycerophosphate at *p*H 5·3. In the normal the neurons of the cranial nerve nuclei only showed staining of the cytoplasm of the nucleolus and of some karyosomes, whereas in the experimental animal the processes from the cells were also stained for a short distance from the cell body.

Vitamin B_1 Diphosphatase *p*H 6·9 and 9·1 : Normal.—When the sections are incubated with aneurin pyrophosphate (vitamin B_1 diphosphate)

they present quite a different picture. The area postrema and both parts of the nucleus solitarius are deeply stained whereas the nuclei of the vagus and the hypoglossus are only lightly stained. In the area itself only a few of the parenchymal cells show activity (Fig. 5). Those parenchymal cells which demonstrated staining show that their cytoplasm as well as their nuclei and karyosomes stained. Between these cells of the conus, the vessels stand out clearly because of the deep staining of the endothelium. The vessels appear at moderate and long incubation periods. The glial cells stain lightly. In the alkaline range the vessels are distinctly stained but in the acid *p*H no vessels at all are seen. The cranial nerve nuclei stained are similar to those found in the acid range. The details of neuronal staining are clearly seen in the large neurons of the cranial nerve nuclei. The cytoplasm and the nucleolus are most deeply stained and the nucleoplasm is consistently a little more lightly stained. Scattered throughout the nucleoplasm is a number of discrete granules of deeply staining material. In the cytoplasm the staining appeared to be deepest in some aggregates of amorphous material. It is difficult to say whether these bodies represented Nissl substance.

Vitamin B_1 Diphosphatase after Cardiazol.—The hydrolysis of vitamin B_1 pyrophosphate is less than the normal control after "cardiazol" convulsions. The difference in staining is seen most clearly at incubation periods of 20 to 30 minutes (Fig. 9). At *p*H 9·1, however, a further difference is seen in the vessels, which, in tissue from animals injected with "cardiazol", stain much more deeply than the definite but lightly stained vessels of the control animal (Fig. 10).

Adenosinetriphosphatase: Normal.—In the material incubated with adenosinetriphosphate, incubation periods of 20 minutes are needed to show even very light staining. The nuclei of the nerve cells and the glial cells of the medulla appear at this length of incubation (Fig. 7). No vessels or other elements are seen to be stained. In the area postrema the nuclei and nucleoli of cells irrespective of type appear.

Adenosinetriphosphatase after Cardiazol.—No alteration in the rate or sites of adenosinetriphosphatase activity was detected in the area postrema after convulsions. Longer incubation periods increased the staining of the nuclei but no new structures could be seen. The parenchymal cells of the conus showed distinct, large, light- to deep-staining nuclei with deeply stained nucleoli. After a 40-minute incubation the nuclei and nucleoli of the cranial nerve neurons are clearly stained but the cytoplasm of the cells whether neuronal or ependymal do not take part in the hydrolysis of adenosinetriphosphate.

Discussion

Histochemically the area shows a consistent and definite pattern of enzyme activity. Adenosine monophosphate is generally hydrolysed in the nerve fibres. It has been shown previously that the cell body is free from any hydrolytic properties for this substrate. Nucleolar staining should, at present, be regarded as a possible artefact of the method. The nucleolus may form a focus of crystallization or have a special affinity for the phosphate freed from the phosphoric acid ester. The area postrema appears to have no nerve fibres and consequently no enzyme activity for adenosine monophosphate.

It is possible that the occasional short fibre, rarely more than one or two in an entire section of the area, may be a nerve fibre with its cell body elsewhere. The hydrolysis of glycerophosphate at *p*H 9·1 shows that this alkaline phosphatase is practically confined to the sinusoidal wall. Much has been written about the role of alkaline phosphatase in glycolysis (Richter, 1951) and in the processes of contractility carried out by proteins (Fell and Danielli, 1943). Its bilaminar arrangement in the intestinal mucosa (Johnson and Kugler, 1953) has given weight to hypotheses concerning the phosphorylation and transport of intestinal glucose. The possibility that the sinusoids of the area postrema may be especially sensitive to metabolites in the blood on the one hand, or to changes in the closely applied parenchymal cells on the other, arises. The direction of the processes assisted by enzyme action in the sinusoidal wall could conceivably be bidirectional: from the blood into the parenchyma as well as from the parenchyma into the circulation.

Examination of the cerebral cortex and other areas showed in earlier work that acid phosphatase at *p*H 5·3 with glycerophosphate as substrate is active strongly in the cytoplasm of neurons. Bodian and Mellors (1944) have shown that the activity of this enzyme increases during the degeneration and regeneration of Nissl substance. The parenchymal cells are not all active in the sections and there is a suggestion that those closest to the sinusoids are most prominent in their staining. As the sinusoidal bed is very dense, this point could not be clarified further. More interesting, however, is the staining of a zone of brain tissue representing the small-celled part of the nucleus solitarius lying between the conus and the vagal and hypoglossal nuclei, called for convenience the intermediate zone. Previous

studies (Naidoo and Pratt, 1951) show acid phosphatase (glycerophosphatase) to be a cytoplasmic enzyme, but this small zone shows staining of cells and tissue between the cells as well. The staining extends from the border of the conus to the vagal and hypoglossal nuclei. The neurons of the vagal and hypoglossal nuclei themselves show the typical cytoplasmic staining observed in earlier studies. Banga, Ochoa, and Peters (1939) found aneurin to be more effective in passing the permeability barriers than the diphosphate, and it is possible that in this form it enters the cells, takes part in the oxidative decarboxylation of pyruvic acid, so that metabolism passes beyond the pyruvate stage. The dephosphorylation of vitimin B_1 diphosphate occurs in the area postrema in both the acid and alkaline ranges. At the alkaline *p*H the vessels as well as the parenchymal cells take part in the dephosphorylating process. The separate identity of glycerophosphatase has already been established. The enzyme hydrolysing glycerophosphate at *p*H 9·1 was shown to be chemically and histologically distinct from the enzyme hydrolysing aneurin pyrophosphate at the same *p*H (Naidoo and Pratt, 1953). Adenosine triphosphate is an energy-rich phosphate. The rupture of the pyrophosphate bonds is now believed to yield considerable quantities of energy. It was previously found that in all regions of the brain the nuclei of cells of all types showed activity in this substrate. The findings for the area postrema do not differ.

After "cardiazol" the cleavage of glycerophosphate in the alkaline range is considerably accelerated whereas the hydrolysis of the same substrate in the acid range is retarded. The increase in alkaline phosphatase activity is restricted mainly to the capillary endothelium where activity normally takes place, whereas the function of acid phosphatase is successively reduced in the area postrema and the intermediate zone depending on the length of convulsions. Aneurin pyrophosphate is broken down more slowly after convulsions than by normal tissue in the acid range, but in the alkaline range an additional factor is that the sinusoids stain more prominently than in the control. It is possible therefore that non-specific alkaline phosphatase activated by "cardiazol" convulsions acts upon aneurin pyrophosphate, breaking it down in the capillaries where the enzyme is situated.

The rest of the medulla seen in each preparation of the area postrema was also studied to exclude the possibility that the differences seen were general differences applicable to the medulla as a whole. Changes in the cells of the reticular formation were not sought. The changes described were limited to the area postrema except for the increased activity of alkaline phosphatase which appeared in the sinusoids of the area postrema as well as in the capillaries of the medulla.

Summary

The effects of "cardiazol" convulsions upon the distribution and activity of enzymes hydrolysing adenosine triphosphate, adenosine monophosphate, aneurin pyrophosphate, and glycerophosphate in the area postrema of the rat are described.

There are clear differences between the cytological enzyme activity observed in the normal animal and in the animal injected with "cardiazol".

The significance of the normal distribution of enzyme activity and of the changes after "cardiazol" convulsions is discussed.

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References

Banga, I., Ochoa, S., and Peters, R. A. (1939). *Biochem. J.*, **33**, 1109.
Bodian, D., and Mellors, R. C. (1944). *Proc. Soc. exp. Biol., N.Y.*, **55**, 243.
Fell, H. B., and Danielli, J. F. (1943). *Brit. J. Exp. Path.*, **24**, 196.
Johnson, F. R., and Kugler, J. H. (1953). *J. Anat.*, **87**, 247.
Meesen, H., and Olszewski, J. (1949). *A Cytoarchitectonic Atlas of the Rhombencephalon of the Rabbit*. Karger, Basel.
Naidoo, D., and Pratt, O. E. (1951). *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 287.
——(1952a). *Ibid.*, **15**, 164.
——(1952b). First Congress of the Histopathology of the Nervous System, Rome.
——(1953). *Enzymologia, Amst.*, **16**, 91.
Richter, D. (1951). In *Recent Progress in Psychiatry*, 2nd ed. Churchill, London.

J. Neurol. Neurosurg. Psychiat., 1954, **17**, 211.

A CASE OF CLINICAL JUVENILE AMAUROTIC IDIOCY WITH THE HISTOLOGICAL PICTURE OF ALZHEIMER'S DISEASE

BY

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The clinical picture of juvenile amaurotic idiocy was originally described in Norway by Stengel in 1826. He observed four siblings with normal development up to the age of 6 years when amaurosis and subsequent mental disorders developed. From the age of 14 years convulsive seizures were noted. The disease ran a progressive course and the patients died at the age of about 20 years. Vogt in Germany in 1905 reported some similar cases and Spielmeyer in 1905 described a typical histopathological picture with globular swelling of the ganglion cells, and balloon-like swellings of the dendrites, due to lipoid deposits in the cytoplasm. In Sweden the disease seems to be relatively frequent. Sjögren (1931) collected 120 cases from 56 families. He examined 4,500 individuals and found a recessive monohybrid heredity. Sjövall and Ericsson (1933) examined biopsy and necropsy specimens from the Swedish cases and described lipoid storage in the cytoplasm of the nerve cells, especially in the cerebral cortex, and also in the Purkinje cells and in the neostriatum. They also pointed out an unusual macroglial reaction with lipoidosis of the glial cells. They found the picture not unlike that seen in normal senescence.

Josephy (1936) advised caution in basing the diagnosis on the clinical picture alone in the absence of a typical histological picture. Sjögren, however, held the opinion that a definite diagnosis could be based on the clinical picture alone, because this was exactly the same from case to case. He emphasized that the disease usually starts at the age of 5 to 8 years with a progressive decrease of vision, leading to complete amaurosis after one or two years. The papillae in the earlier stages are brownish-yellow, later pale yellow or white, often with concentric zones. The retinal vessels, especially the arteries, are narrow, and atrophic areas occur in the eye ground. The pigmentations are granular, increasing toward the periphery. In the final stages a bilateral posterior cataract may develop, and the pupillary reflex is abolished. Increasing dementia is a constant feature with disorders of the different intellectual spheres including understanding, memory, and judgment. There may be emotional lability with seizures of weeping and unmotivated laughter. The behaviour varies between laziness and restlessness but the patient is often able to obey orders. In a more advanced stage postural anomalies appear, with general weakness, kyphosis, genu valgum, and pes planus. The gait becomes unsteady and shuffling, and the patient may move for a time in one spot before starting to walk with the feet apart and dragging on the ground. There is a slow intention tremor involving the entire body when the patient starts walking (*démarche trepidante*). The speech becomes slurred, stuttering, and monotonous, and there is paucity of words and agrammatism. Facial mimicry is lost. The hearing is good; the reflexes are normal or increased. An oily appearance of the face and acrocyanosis indicate disturbed vegetative functions. Epileptic fits may sometimes be observed early, but usually not until the blindness has become manifest. In the later stages contractures, rigidity, fibrillary muscular tremor, and decubitus follow, and the patients die from intercurrent diseases.

In Norway juvenile amaurotic idiocy is rare. By questioning all mental hospitals and blind schools 10 cases have been found, including the patient reported here, and his brother.

Case Report

The patient was admitted to Reitgjerdet Mental Hospital on October 6, 1945, at the age of 14 years. His parents were first cousins. There was no history of mental disease in the family as far back as his great-great-grandparents with the exception of the patient's older brother, who apparently had suffered from the same disease and died from an intercurrent disease at the age of 13 years. One sister died of pneumonia at the age of 15. Another brother, who was more than 20 years old, was alive and healthy.

The patient developed normally up to the age of 6, when impairment of vision and retarded mental development were noted. He attended school for one year but then had to be taken away because he was no longer able to read. He had by then learnt how to spell and put words together, but this was soon forgotten. He stayed at home on the farm with his father, and at times he was excited and difficult to handle. At the age of 13 years a convulsive seizure was observed, and several seizures occurred at varying intervals during the following years. His speech became less distinct, and a tendency to perseveration was noted. On admission to the hospital he was disoriented as to time, place, and situation. He knew his own name, gave short answers to simple questions, but was deeply demented. He was anxious when examined, resistive, and emotionally labile. Communication with the patient was difficult; sometimes he behaved calmly, but at other times he was restless and crying. He used to hide his head under the blankets, and had to be helped and nursed.

He looked well nourished. Acrocyanosis and marked dermographism were noted. Temperature and pulse rate were normal. His sleep was normal. The blood pressure was 100–125/70–90 mm. Hg. Blood examinations showed slight lymphocytosis, later marked eosinophilia (25% eosinophils) and leucocytosis (12,000 leucocytes). The sedimentation rate varied between 20 and 32 mm. There was no evidence of disease of the internal organs. Serological examinations of blood and cerebrospinal fluid gave normal findings. Cholesterol values were not determined because of technical difficulties. The electrocardiogram was normal. Ophthalmological examination showed marked mydriasis, and a sluggish pupillary reflex. He was able to distinguish large objects at a short distance. The papillae were pale, distinctly marginated, surrounded by a yellowish, waxy-looking zone. The arteries were narrow, and along them small granulated pigmentations without dendrites were observed. The maculae were not visible, and there was no cherry red spot.

FIG. 1.—The patient.

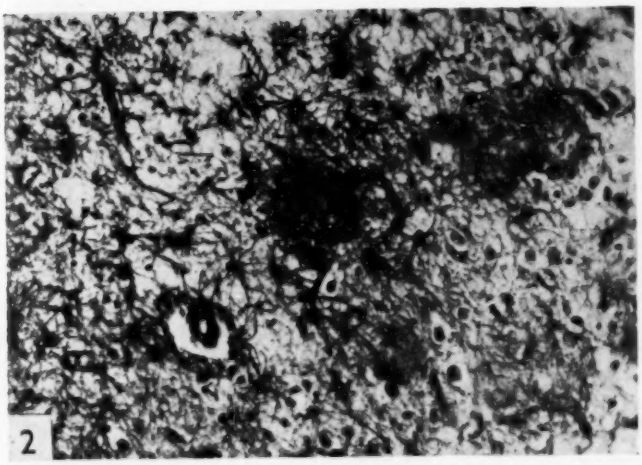
Neurological examination disclosed slightly disturbed coordination, but no definite ataxia. Tactile sensation was impaired all over the body. The speech was slurred and difficult to understand, but there was no definite dysarthria. He kept his head and shoulders bent forward, and his knees were flexed (Fig. 1). The gait was unsteady. The reflexes of the upper and lower extremities were exaggerated, especially the patellar reflexes. The abdominal reflexes were present, and also the plantar reflexes. During his stay in hospital he had a few epileptic fits.

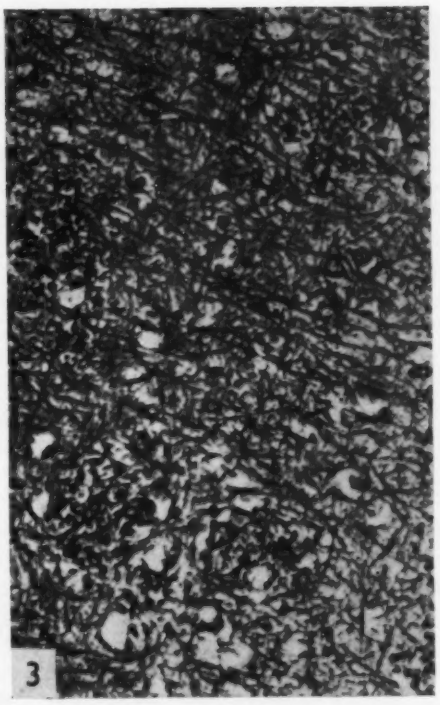
He became more and more helpless, demented, and untidy. Finally he was entirely confined to bed and died of bronchopneumonia on April 5, 1948.

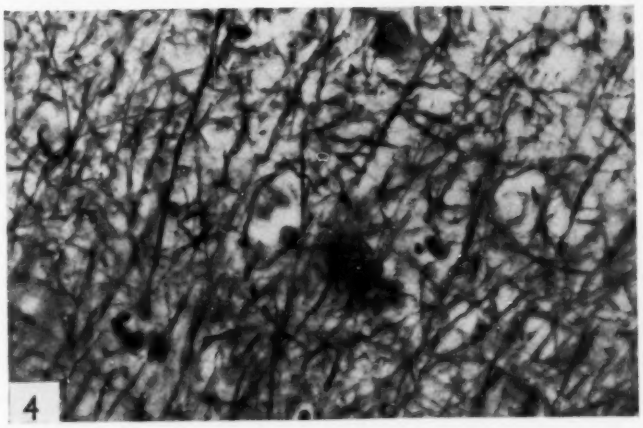
Necropsy.—Necropsy showed no gross pathological changes except pneumonia. Microscopical examination of the liver showed some lipoid storage.

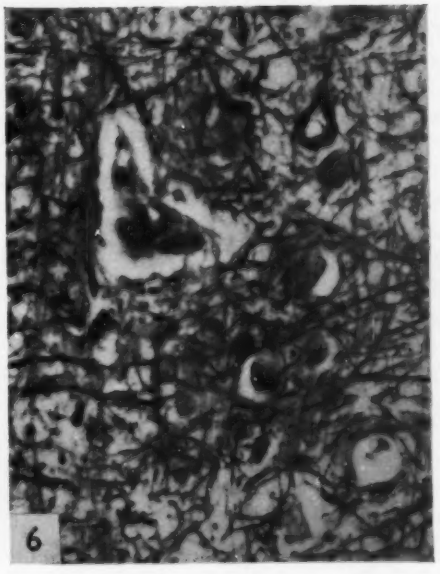
The Brain.—When examined the brain had been stored in formalin for nearly four years. The total weight was 850 g. The cerebral hemispheres appeared evenly atrophied, while the cerebellum seemed to be of normal size. The cerebral gyri were narrow. and the sulci widened. The lateral ventricles were enlarged. The cortical surface appeared smooth, and on the cut surface the atrophy was mainly restricted to the white matter. Blocks from representative parts of the brain, cerebellum, and brain-stem were embedded in paraffin, stained with haematoxylin and eosin, thionin, Holzer glial fibre method, Bodian's silver method, and Loyez's method for myelin. Supplementary blocks were frozen and sections stained with Sudan III.

Microscopical Examination.—The leptomeninges and the vessels showed no pathological changes. The cortical pattern was quite well preserved, while there was a moderate and diffuse loss of nerve cells without preference for any special layer. The neurons were slightly irregular and their cytoplasm was shrunken, while the nuclei looked normal. The Nissl granules were mostly well stained. In some of the cells there was a moderate amount of sudanophil material, but no balloon-like swelling of the cells was noted in any part of the brain. The various areas examined all showed similar pictures, but certain parts such as the hippocampal formation were more severely involved. Neuronal changes of the same kind were also observed in the basal ganglia, striatum pallidum, and thalamic nuclei. The cells were rather small and irregular. In the hypothalamic nuclei and the nuclei of the brain-stem the neurons showed similar changes. The cerebellum was apparently intact. The Purkinje cells were nicely pear shaped, and there was no swelling of their dendrites. The dentate and the roof nuclei were normal. The glial elements were increased in number. There were numerous small elongated cells with irregular nuclei, resembling microglial cells, and also a great number of large astrocytes. In thionin sections, rounded, pale blue patches were scattered throughout the cortex, especially in the outer three layers. Holzer staining showed that these patches were made up partly by glial fibrils, and partly by a more densely staining ground substance (Fig. 2). With silver staining some of the patches were impregnated, and gave the picture of senile plaques (Figs. 3–4). Some of the microglial cells









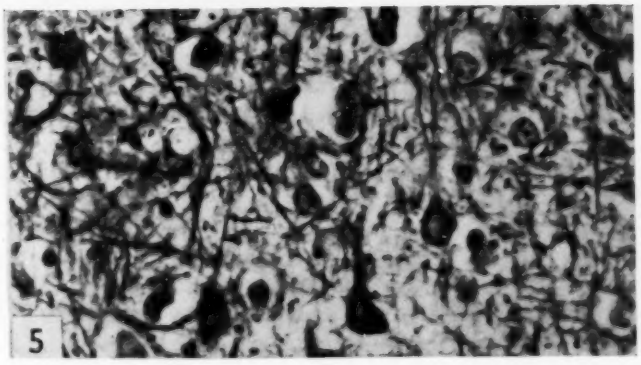


FIG. 2.—Dark-staining patches in the cortex partly consisting of glial fibres and partly due to a heavier staining of the background. Holzer. × 200.

FIGS. 3 and 4.—Senile plaques in the cortex. Bodian's silver method. × 200 and × 400.

FIGS. 5 and 6.—Alzheimer's fibrils in cortical neurons. Bodian's silver method. × 400.

contained sudanophil granules. Compound granular cells were few and only seen perivascularly in the white matter. There was a moderate loss of myelin in the white matter, and an increase of fibrillary glia. In the globus pallidus a few mulberry-shaped, iron-containing concretions were present in the perivascular spaces, and some of the arteries also contained iron deposits in their walls.

With Bodian's silver impregnation a great number of curved, thick intraneuronal fibres of the Alzheimer type

were seen throughout the cerebral cortex (Figs. 5, 6) but neither Alzheimer fibrils nor senile plaques were seen in the subcortical grey matter or cerebellum.

Discussion

The clinical picture in the present case was almost identical with that of juvenile amaurotic idiocy described by Sjögren. Of other possible diagnoses a syphilitic disease was considered, viz., either a juvenile general paralysis or a congenital form of neurosyphilis. These diseases may also be combined with papillary atrophy and retinal pigmentation. The papillae, however, are usually less distinctly marginated and the pigmentations darker. There may be posture anomalies, although spastic paretic contractures will usually predominate, with extra-pyramidal symptoms being less distinct. Serological tests were all negative.

In view of the rapid progression of the disease a diagnosis of degeneratio pigmentosa retinae with mental defects did not seem justified. The lack of pressure symptoms did not indicate hydrocephalus as the cause of the symptoms. Familial diffuse sclerosis of the Pelizaeus Merzbacher type, besides amaurosis and epilepsy, always includes spastic ataxic paralyses and spastic contractures. The cerebellar heredoataxia of Pierre Marie shows similar walking disturbances, but here cerebellar symptoms will always predominate. The lack of the cherry red spot and the relatively slow course made us reject also the congenital form of amaurotic idiocy.

The histological picture, however, was quite different from what was expected according to the clinical findings. Neuronal changes typical of amaurotic idiocy were not present, although some lipoid storage was observed. This, however, might be a result of any degenerative process, and may even be seen in senescence.

The general impression was indicative of a slowly progressing degenerative disease, primarily affecting the cerebral cortex, but also involving the nerve cells of the basal ganglia and the brain-stem. The absence of similar changes in the cerebellum was rather surprising. The moderate demyelinization was considered secondary to the neuronal disease. The presence of Alzheimer fibrils and the number of senile plaques throughout the cortex are unusual at this age.

A somewhat similar case has been described by Malamud and Lowenberg (1929) A man died at the age of 24 years from a disease which apparently had started very early following an attack of scarlet fever. His development was retarded, and when he was 14 mental deterioration became apparent. Later, both mental and physical symptoms progressed. The authors described both Alzheimer fibrils and senile plaques in the cerebral cortex, but none in the cerebellum. They concluded that the Alzheimer symptom complex could not be confined to any particular age, and also that several aetiological factors are capable of producing similar pictures.

Lüers (1947) described a juvenile form of Alzheimer disease in a brother and a sister. The clinical diagnosis was multiple sclerosis. The symptoms started at the ages of 26 and 43 years, respectively. Lüers referred to a paper by von Braunmühl who found that the earlier Alzheimer's disease starts, the more atypical is the course.

Hallervorden (1935) reported Alzheimer changes in post-encephalitic brains in a total of 35 cases described by himself and others, the age of the patients varying between 11 and 60 years. He did not observe any senile plaques. He was of the opinion that fibrillary changes occurred only in chronic diseases, and were possibly due to colloid-chemical processes leading to degeneration.

Meyer (1949) found a combined systemic disease in two sisters, 7 and 4 years old, with clinical cerebral palsy and idiocy. He found senile plaques in the dentate hilum, but no fibrillary changes.

Jervis (1952) reported the case of an 11-year-old child with mental deterioration from birth, displaying a cherry red spot as in congenital and infantile forms of amaurotic idiocy. There were senile plaques in the cerebellum, and no real ballooning or swelling of cells and dendrites.

Van Bogaert (1952) reported on a family with tardive dementia combined with extrapyramidal features, which displayed histologically the picture of amaurotic idiocy although the lipoid storage was very moderate and the cell forms not quite typical. He also referred to a communication by Hallervorden who had seen a case of late lipoidosis combined with Alzheimer's fibrillary changes.

As to amaurotic idiocy, a congenital, an infantile, a late infantile, a juvenile, and late forms have been described, the last by Kufs (1931). Histological lipoidosis may consequently be seen at any age. On the other hand Alzheimer's fibrillary changes and senile plaques have been described in young subjects displaying a number of different clinical pictures.

The amaurotic idiocy has a somewhat different clinical symptomatology in its different age groups, the cherry red spot belonging to the youngest age group, the visual disturbances being more or less absent in the late forms, and the progression slower in the older groups. Perhaps the histological picture is even less pronounced in these late cases.

Alzheimer's fibrillary changes have been found as an associated feature in amaurotic idiocy, and they have been described in subjects of different ages including children.

In the present case the clinical course was that of a classical juvenile amaurotic idiocy, while the histological pictures were suggestive of early Alzheimer disease. It is obvious that a slowly progressing degenerating disease caused the symptoms, but the question of whether the disease should be considered amaurotic idiocy or a juvenile form of Alzheimer's disease is left open.

Summary

A case of clinical juvenile amaurotic idiocy is reported. The gross and microscopical pictures of the brain are described. Histological sections failed to disclose swollen nerve cells as in lipoidosis, and a diffuse cortical atrophy with Alzheimer's fibrillary changes in the ganglion cells and numerous senile plaques were found.

References

Bogaert, L. van (1952). *Dtsch. Z. Nervenheilk.*, **168**, 267.
Hallervorden, J. (1935). *Ibid.*, **136**, 68.
Jervis, G. A. (1952). *J. Neuropath.*, **11**, 4.
Josephy, H. (1936). ed. Bumke, O., and Foerster, O. *Handbuch der Neurologie*, vol. 16, p. 394. Springer, Berlin.
Kufs, H. (1931). *Z. ges. Neurol. Psychiat.*, **137**, 432.
Lüers, Th. (1947). *Arch. Psychiat. Nervenkr.*, **179**, 132.
Malamud, W., and Lowenberg, K. (1929). *Arch. Neurol. Psychiat., Chicago*, **21**, 805.
Meyer, J. E. (1949). *Arch. Psychiat. Nervenkr.*, **182**, 731.
Sjögren, T. (1931). *Hereditas, Lund.*, **14**, 197.
Sjövall, E., and Ericsson, E. (1933). *Acta path. microbiol. scand.*, Suppl. 16, 460.
Spielmeyer, W. (1905). *Nissls Beitr.*, **2**, H, 1. Cited by Josephy.
Stengel, E. (1826). *Eyr et medicinsk Tidsskrift, Christiania*, **1**, 347.
Vogt, H. (1905). *Mschr. Psychiat., Neurol.*, **18**, 161, 310. Cited by Josephy.

J. Neurol. Neurosurg. Psychiat., 1954, **17**, 216.

SYMPTOMS OF ANXIETY AND TENSION AND THE ACCOMPANYING PHYSIOLOGICAL CHANGES IN THE MUSCULAR SYSTEM

BY

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It has already been shown that anxiety is often accompanied by muscle over-activity (Jacobson, 1938). Malmo and Shagass (1949a) found that the amplitude of action potentials recorded from the neck muscles of patients with anxiety states was significantly higher than in healthy controls when both were stressed by applying painful stimuli to the forehead; but the action-potential ratings also correlated with movements drawing the head away from the stimulus. Malmo and Shagass (1949b) used the same technique when they found that anxious patients with head complaints had significantly more activity in the neck muscles during stress than those without. Wolff (1948) also recorded over-activity in the electromyograms of the neck and scalp muscles of anxious patients. When the anxiety was diminished the over-activity and the headache disappeared. Finally, Holmes and Wolff (1952) found that patients with backache had pain and a generalized over-activity of the trunk muscles in situations which engendered conflict and insecurity, or feelings of hostility, frustration, and guilt. As the findings in the last two papers were presented in the form of typical case histories it was not possible to estimate how regularly headache or backache and muscular over-activity were associated.

We aimed, by means of controlled experiments, to study the relations between the symptoms complained of by anxious patients and the activity in the skeletal muscles. In order to limit the experimental conditions to the simplest we measured the muscle activity occurring in our subjects when they were relaxing, remaining still, and, where possible, in a position which avoided reflex postural tone in the muscles being investigated. The activity recorded under these conditions we called muscle tension.

Our hypotheses were first, that an increase in innervation of the skeletal muscles accompanies anxiety so that in anxious patients attempting to relax not only will muscle tension be greater than in healthy subjects, but those patients with most clinical evidence of anxiety and "tension" will have the most muscle tension. It follows that the increase in muscle activity expected in the anxious would be evident in a number of well separated groups of voluntary muscles.

Secondly, that the physiological mechanism underlying some of the common symptoms of anxiety is increased muscle tension, so that more muscle tension would be recorded in muscles in which such symptoms were felt than in those where they were not.

Subjects

Thirty-two consecutive patients were investigated. The records of two had to be discarded as they were spoiled by electrical artefacts. Of the remaining 30, 10 were male and 20 female, and their mean age was 39·5 years, ranging from 27 to 58 years. Fifteen were diagnosed as cases of anxiety states; one of these was also an alcoholic. Thirteen were of depression with anxiety and "tension", one of whom was also suffering from anorexia nervosa, and there were two patients with obsessional neuroses and marked anxiety.

Method

The patients' symptoms of anxiety and tension were scored by means of an inventory based on Cameron's analysis (1944) of the patterns of anxiety and on the results of a survey by one of us (J.G.G.) in which 29 senior psychiatrists were presented with a questionnaire designed to elicit and to afford a basis for discussion of the clinical observations by which they ascribed "tension" to a patient. Those items which the majority were agreed upon were included in the present inventory.

The inventory was completed in the course of an interview given during the recording in which the patients were encouraged to describe their symptoms freely. Each positive item entered was accompanied by the patient's verbatim account.

The inventory was divided into three parts. The first assessed the patient's affective state, his reports

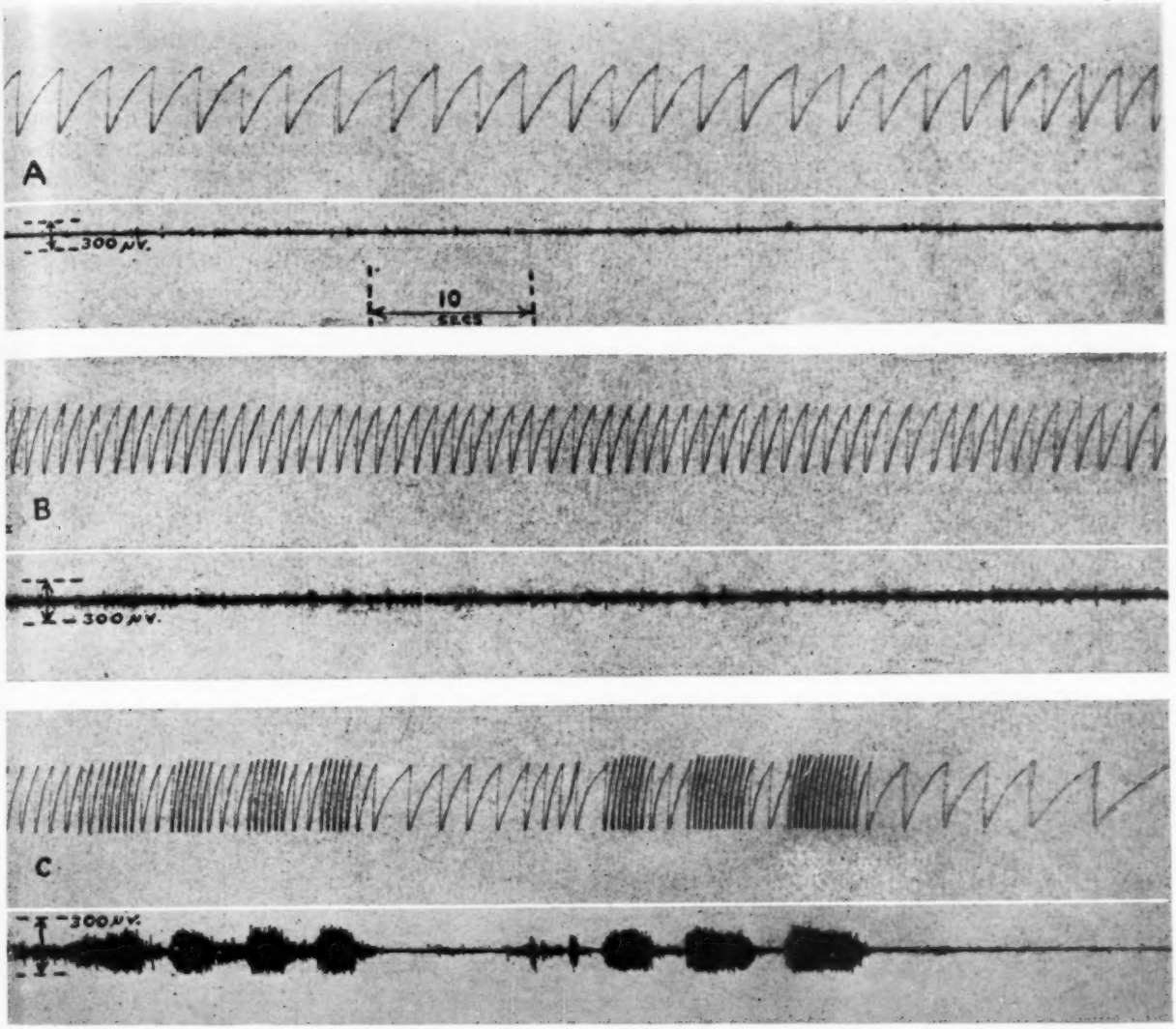

FIG. 1.—Three records (one minute approximately) to show counts (upper tracing), and action potentials (lower tracing).
A—Relaxing : moderate muscle tension.
B—Increase in muscle tension following interview.
C—To show effect of movement of arms : compare this erratic record with the regular tension in A and B.

of his feelings of anxiety and tension : he was asked if he felt tense and unable to relax, anxious and apprehensive, irritable and touchy, restless and fidgety, and whether on edge and keyed up at the present moment. The first three of these items were scored nil, 1 or 2, the remaining two as either absent or present (nil or 1). The latter method of scoring was adopted when marking the second part of the inventory which recorded the presence now, or frequently during the past 10 days, of bodily symptoms believed to be muscular in origin : headache or head sensations now ; aching, feelings of stiffness, or drawing sensations in neck, arms, back, or elsewhere ; tremulousness, starting, or waking up with a sudden jerk. The items placed in the last part of the inventory were symptoms which have also been claimed to be manifestations of muscle over-activity, but with less certainty. They were undue fatigue, a sense of moving awkwardly or stiffly, sensations of numbness and fluttering, and visual disturbances.

In the subsequent calculations we used (*a*) the total score obtained from the whole inventory, (*b*) that part giving a score of the patient's feelings of tension and anxiety, or (*c*) the muscular symptoms score, depending on which of these we required to relate to muscle tension (Table I).

Muscle activity was measured by means of a two

TABLE I

THE INCIDENCE OF SYMPTOMS ENUMERATED IN THE INVENTORY GIVEN TO 30 PATIENTS WITH ANXIETY AND TENSION STATES

Symptoms	Complaints	Incidence (No.)	Incidence (%)
From which the scores of the patient's feeling of anxiety and tension were obtained	1. Tense, unable to relax, on edge, etc.	30	100
	2. Anxious, apprehensive	29	96
	3. Irritable, touchy	22	73
	4. Restless, fidgety	24	79
	5. Tense during recording	22	73
From which the scores of bodily symptoms attributable to sustained muscular over-activity were obtained	1. Headache while recording	7	22
	2. Arms ache or stiff	13	43
	3. Neck aches or stiff	19	63
	4. Back aches or stiff	16	53
	5. Aches or stiffness in other bodily areas	20	66
	6. Tremulousness	15	50
	7. Starts unduly, wakes with a jerk	19	63
Additional symptoms which contributed to the scores for the total clinical manifestations of anxiety and tension	1. Undue fatigue	23	76
	2. A sense of stiff, clumsy or unfree movement	21	69
	3. Sensations of numbness, fluttering, etc.	10	33
	4. Visual disturbances	12	40

channel electromyograph (E.M.G.) with a specially designed integrating circuit.* In each channel the muscle potentials were fed from a preamplifier first to an oscilloscope visible to the operator ; this enabled him to monitor the record, ensure its freedom from artefact, and to observe whether the record was of the pattern to be expected from a tense muscle, namely, an evenly sustained interference pattern of muscle potentials, free from the sudden high-voltage bursts of activity produced by movements ; secondly to a pen recorder which made a permanent tracing. Finally, the action potentials were summed in an electronic integrating circuit which operated two electromagnetic counters.

Calibration tests showed that the rate of counting bore a linear relation both to the frequency of the input when the voltage was constant and to the input voltage when the frequency was constant. The counts obtained from a muscle, therefore, would be proportional to the number of motor units contracting, which determines the amplitude (voltage) of the signals picked up, and to the frequency at which they are contracting. Fig. 1 illustrates three typical tracings, about one minute in duration, of the action potentials and counts obtained from the left forearm of an anxious patient. In tracing A he is attempting to relax but

* We are indebted to the designer, Mr. Peter Styles of St. Thomas's Hospital, who constructed the electromyograph, and to Professor A. J. Lewis, the Director of Research, and Mr. Furneaux, Psychologist in Charge of the Nuffield Research Unit at this Institute, who drew up the specifications for it.

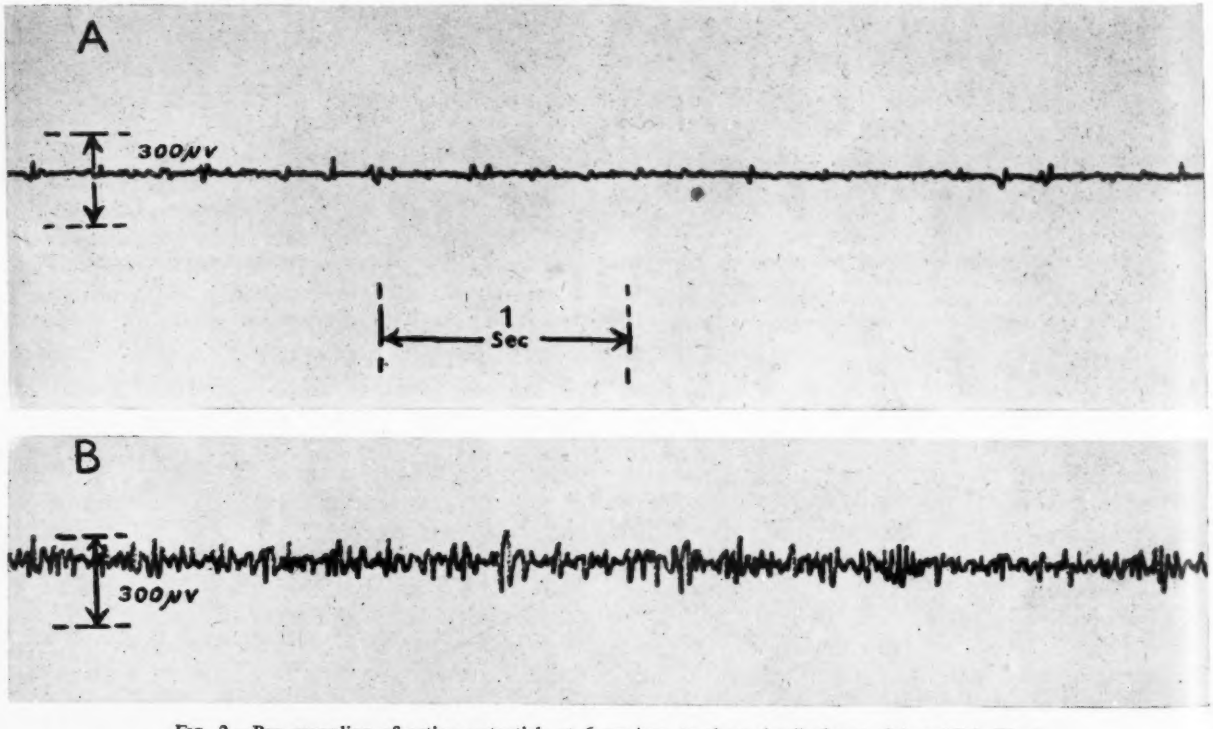

FIG. 2.—Pen recording of action potentials at 6 cm./sec. to show detail of part of A and B in Fig 1.

shows moderate muscle tension (24 counts a minute); in B he is still relaxing but activity has increased following a disturbing interview (55 counts a minute). In both A and B the action potentials are regularly sustained (muscle tension); for comparison, C shows the erratic tracing which accompanied gestural movements of the arm during interview. Fig. 2 shows details taken from A and B which were recorded simultaneously by a pen recorder at 6 cm. a second.

The method of scoring adopted was to record the counts from both channels at minute intervals, and in the subsequent calculations to take the mean of the minute scores.

Procedure

The patients lay on a standard hospital bed, their skins were cleaned with spirit, briskly rubbed with electrode jelly and surface electrodes applied. The latter were silver cups 1 cm. in diameter, filled with electrode jelly, and strapped on with adhesive plaster. Those from channel 1 were placed over the crests of the left forearm extensors, and those from channel 2 over the frontalis above the centre of each eyebrow. A saline pad on the right leg was used as an earth. The patient was reassured, then told to remain as still as he comfortably could, to relax as far as possible, and to close his eyes. Previous trials had indicated that seven minutes was the most suitable period of relaxation. He was then interviewed for about 20 minutes; during this time the inventory was completed. Then a second relaxing period of seven minutes was recorded in a similar manner to the first.

The first 15 patients were seen on a second occasion when recordings were obtained from the posterior cervical muscles and the extensors of the left foot. For these recordings the electrodes were small rubber sponges soaked in saline and containing a loop of silver wire. The patient sat in a chair and was instructed to relax and look at a piece of grey paper 4 inches square placed at arm's length and at eye level. Satisfactory, movement-free recordings were obtained while relaxing for seven minutes.

The reliability of the method was estimated by the test-retest procedure. The product-moment correlation between the scores for the initial and final seven minutes of relaxation in the 30 patients of this study was $0{\cdot}90 \pm 0{\cdot}023$ for the arms, and $0{\cdot}94 \pm 0{\cdot}002$ for the forehead. We concluded from these findings that reliable scores are obtained by this method, and that the patients were characterized by a high degree of constancy of muscle tension from one moment to another.

Results

Muscle Tension in Healthy and Anxious Subjects.—A preliminary investigation was made to test the hypothesis that an increased innervation of the voluntary muscles is a physiological accompaniment of anxiety by comparing muscle tension in anxious and healthy subjects. It was expected that this experiment would also give an indication of the sensitivity of the electromyographic method in discriminating between levels of muscle tension.

The muscle tension recorded from m. frontalis of 26 patients diagnosed as anxiety states, and of 30 healthy soldiers was measured while they relaxed with their eyes closed as described above. The mean muscle tension score of the former was 9·59 counts/min. (S.D. 5·14) and of the latter 5·23 counts/min. (S.D. 3·01). On testing for a significant difference t was found to be 3·86, which is highly significant ($P > 0{\cdot}001$). The anxious patients, therefore, showed more muscle tension than the healthy subjects and the method discriminated well between the two groups.

Character and Frequency of Symptoms of Tense, Anxious Patients.—The frequency of the complaints enumerated in the inventory is summarized in Table I. It follows from the method of selecting the patients that complaints of feeling tense and anxious would be very common in them. In fact, all the patients complained of feeling tense, and 22 experienced it even while they "relaxed" on the bed at the time of the recording; 29 were feeling anxious. The complaints of feeling restless and irritable were also very common.

When each patient was asked to describe further his feeling of tension, 24 depicted it as a bodily sensation in one or more of the following terms: "A feeling of tightness, as if muscles taut", "whole body tightens up and pains when I am worked up", "tight as if drawn up", "a drawing up or dragging feeling", "a stiffness of the muscles", "stiff all over", "as if made of iron—all muscles immovable", "a soreness or bruised feeling", "cramped", "unable to relax my body". Twelve of these described tension as something experienced exclusively in their muscles while six others experienced it solely as a state of feeling. They used such phrases as "on edge", "keyed up", "over-alert all the time", "tensed up as if I wanted to scream", "jittery and unable to settle".

Many of the patients asserted that their primary complaint of "tension" was attributable to the unrelaxed or contracted state of their muscles (79%), that they felt relief from this state with barbiturates or when relaxing in a hot bath (59%),

and that they had observed a close relationship between the intensity of this feeling of tension and emotionally disturbing experiences (50%).

Relations between Symptom Scores and Measures of Muscle Tension.—A comparison was made between the muscle activity in patients with most clinical evidence of tension and anxiety, and in patients with the least.

The patients were divided, therefore, into two groups by taking the scores they obtained on the whole inventory of their symptoms and finding the median. The means of the muscle tension scores (measured by the E.M.G.) were calculated for those above and below the median. A t-test showed differences between the mean scores of muscle tension in the two groups at the following levels of significance; 0·025 for the frontalis, 0·05 for the forearm extensors, and 0·01 for the combined frontalis and arm scores (Table II).

The median of the scores of the patients' reports of their feelings of tension and anxiety (part 1 of inventory) was found, and again the means of the E.M.G. muscle tension scores of those patients above and those below the median were tested for significant differences. The mean muscle tension in the forearm extensors, in the frontalis, and in the two combined were greater in the patients who felt more tense. The levels of significance were 0·05, 0·01, and 0·0025 respectively (Table II). Having found this association an attempt was made to assess its intensity by correlating the patients' scores of their feelings and their total muscle tension scores. The product-moment correlation ($r = 0·45$) was significant.

Finally, the combined muscle tension and the arm muscle tension of patients with more than the median scores for bodily symptoms attributed to muscular over-activity (part 2 of the inventory) were significantly greater than those with less. The muscle tension in the forehead did not differentiate the two groups, but the product-moment correlation between scores for bodily symptoms and for muscle tension was significant ($r = 0·49$).

It may be concluded, therefore, that those patients with more than the median number of clinical manifestations of tension and anxiety showed significantly more muscle action potentials of a pattern to be expected where the muscles are in a condition of sustained contraction than did patients with less than the median score. It was therefore possible to differentiate between the more and the less muscularly tense patients by scoring the items describing their feelings of tension listed in the inventory; but the items in the inventory dealing with the bodily symptoms of muscle over-activity served to discriminate only between those with and those who had no such muscle tension in the forearm muscles.

The Relation between Certain Bodily Sensations and Muscle Tension.—Certain bodily sensations were studied.

Headache and Head Sensations.—At the time of recording seven of the 30 patients complained of headache or head sensations which they described as follows: "tight band across head—a pressure band", "pressure and tightness across forehead which becomes painful if I am tensed up", "a soreness and bruised feeling at the top and back of the head that comes on with keyed-up feelings", "a dull ache or dragging pain spreading from back

TABLE II

DIFFERENCES IN E.M.G. MUSCLE TENSION SCORES OF ANXIOUS PATIENTS WITH CLINICAL SCORES OF TENSION ABOVE AND BELOW THE MEDIAN

Muscle Tension		Clinical Manifestations of Tension and Anxiety Recorded on the Inventory								
		Total Symptom Scores			Feelings of Anxiety and Tension Scores			Muscular Symptom Scores		
		Above Median		Below Median	Above Median		Below Median	Above Median		Below Median
	No.	14		12	9		14	14		11
Total Forehead and arm	Mean E.M.G. Scores	31·12		13·58	33·77		14·13	31·48		17·78
	σw		6·99			6·03			4·66	
	t		2·51			3·26			2·94	
	P		0·01			0·0025			0·005	
Frontalis	Mean E.M.G. Scores	21·83		9·68	23·58		9·74	21·24		13·92
	σw		5·53			5·10			6·35	
	t		2·19			2·71			1·15	
	P		0·025			0·01			N.S.	
L. forearm extensors	Mean E.M.G. Scores	9·32		3·90	10·19		4·39	10·24		3·86
	σw		2·72			3·07			2·88	
	t		1·99			1·89			2·12	
	P		0·05			0·05			0·025	

P = The probability corresponding to the single-tailed or asymmetrical t-test (Fisher's tables).

of neck to eyes ", " a sort of tightness—dull ache ". Six said that their head complaints increased when they were disturbed and tense, and five had noticed that sedatives or relaxing in a hot bath relieved them; another patient observed that crying relieved her symptoms.

The muscle tension in the frontalis was measured while the patients relaxed on a bed with their eyes shut. When the mean of the E.M.G. frontalis scores of the seven patients with headaches was compared with the mean of the scores of those without headaches, the difference was found to be highly significant. The probability that the higher activity in the headache group could be attributed to chance was less than 1 : 400 (Table III).

One patient developed a headache during the recording. The counts per minute during seven minutes relaxing without headache were 30; this increased to 85 when the headache was present in the final seven-minute relaxing. Two other patients began the recording with headaches which disappeared during the interview. In both cases the muscle tension score in the second relaxing period was very significantly lower, having dropped by 6 and 8·5 counts per minute. The graph in Fig. 3 illustrates the first of these cases.

A difference in muscle tension between those with and without headache was found only in the frontalis muscle; the forearm muscle tension of the two groups was not significantly different. In these cases, therefore, the increase in muscle tension tended to be localized to, or to predominate in the muscles supposedly giving rise to the symptom. This interpretation is corroborated by the analogous findings in those patients who complained of arm symptoms.

Arm Symptoms.—Fourteen patients complained of stiffness, " rheumatics " (without joint pains), and aching in the arms. Some of these commented that their arms were tensed or tightened up, cramped, or subject to drawing feelings. In only three patients were these symptoms present while they relaxed on the bed during the recording. The muscle tension in the extensor muscles of the left forearms of these 14 patients was significantly higher ($P = 0{\cdot}0025$) than that recorded from the 16 patients without symptoms referrable to the arms. There was no significant difference in the frontalis tension in these two groups of patients, that is to say, tension was again localized to the bodily area of the symptom.

Tremulousness.—This symptom is considered here because the tremulousness was often referred to the arms in addition to being experienced as a generalized shakiness. It was of interest to find, therefore, that the 15 patients with this complaint had a significantly greater muscle tension in the arm extensors and in the frontalis than had the remaining 15 who were not tremulous (Table III). As far as it is justified to argue from an investigation limited to two bodily areas, the increase in muscle tension in tremor due to emotion is widespread.

Neck Symptoms.—Recordings were obtained from the posterior cervical muscles of 15 patients, four of whom complained of pain or stiffness in the neck. These four showed a significantly greater level of muscle activity than did the 11 without neck

TABLE III

ASSOCIATION BETWEEN BODILY SYMPTOMS ATTRIBUTABLE TO MUSCLE TENSION AND DIRECT MEASURE OF MUSCLE TENSION IN VARIOUS AREAS

Muscle Tension		Symptoms of Pain and Tightness in										Other Symptoms			
		Head		Arm		Neck		Back		Other Areas		Tremor		Startles	
		With	Without	With	Without	With	Without	With	Without	With	Without	With	Without	With	Without
	No.	7	23	14	16	19	11	17	13	10	20	15	15	19	11
Frontalis	Mean E.M.G. Scores	31·26	11·79	21·08	12·18	16·19	16·57	16·79	15·74	15·02	14·06	21·19	11·48	20·12	9·79
	σw	5·48		5·34		4·86		5·64		5·28		5·27		5·47	
	t	3·55		1·67		0·07		0·19		0·18		1·82		1·89	
	P	0·0025		N.S.		N.S.		N.S.		N.S.		0·05		0·05	
Arm	Mean E.M.G. Scores	9·40	6·10	10·78	3·46	8·16	4·65	7·32	6·29	4·12	3·57	9·56	4·19	8·60	3·90
	σw	3·12		2·32		2·72		2·71		2·55		2·41		2·66	
	t	1·06		3·16		1·29		0·38		1·61		2·23		1·77	
	P	N.S.		0·0025		N.S.		N.S.		N.S.		0·025		0·05	
Neck	Mean E.M.G. Scores	—	—	—	—	38·65	11·97*	—	—	—	—	—	—	—	—
	σw	—	—	—	—	7·51		—	—	—	—	—	—	—	—
	t	—	—	—	—	3·55		—	—	—	—	—	—	—	—
	P	—	—	—	—	0·0025		—	—	—	—	—	—	—	—

P = The probability corresponding to the single-tailed or asymmetrical t-test (Fisher's tables).
* In this instance N = 15, four with neck complaints and 11 without.

symptoms. The muscle tension in the forearm muscles was not significantly different in the two groups with and without neck symptoms, nor was the muscle tension in the frontalis. So again the principal increase in muscle tension was in those muscles to which the symptom had been ascribed by the patient (Table III).

Backache.—Seventeen patients complained of aching, stiffness, or tightness in the back. Neither in the forearm muscles nor in the frontalis was the muscle tension in these cases greater than in those without backache. No recordings were made from the back. The negative findings are, nevertheless, consistent with the tendency observed above for muscle tension to predominate in the muscles in which the patient feels the symptom.

Aches and Stiffness in Other Bodily Areas.—Ten patients complained of aching in the shoulders, jaw, legs, etc., which was associated with emotional disturbance. But they also could not be differentiated from the remaining 20 by recording the muscle tension in the forehead and forearm. In one patient, however, who complained of tenseness principally in the face and jaw, very high counts were obtained when electrodes were placed on the masseters.

Starts Unduly or Wakes with a Sudden Jerk.—A significant difference (at the 5% level) was obtained between the means of the muscle tension scores obtained from the arms and the foreheads of the 19 patients who admitted to having this symptom and the mean scores of 11 who did not. This finding is consistent with the view that the tendency to start increases when the muscles are in a state of contraction.

Other Symptoms Included in the Total Inventory.—Undue fatigue, feelings of clumsiness and unfree

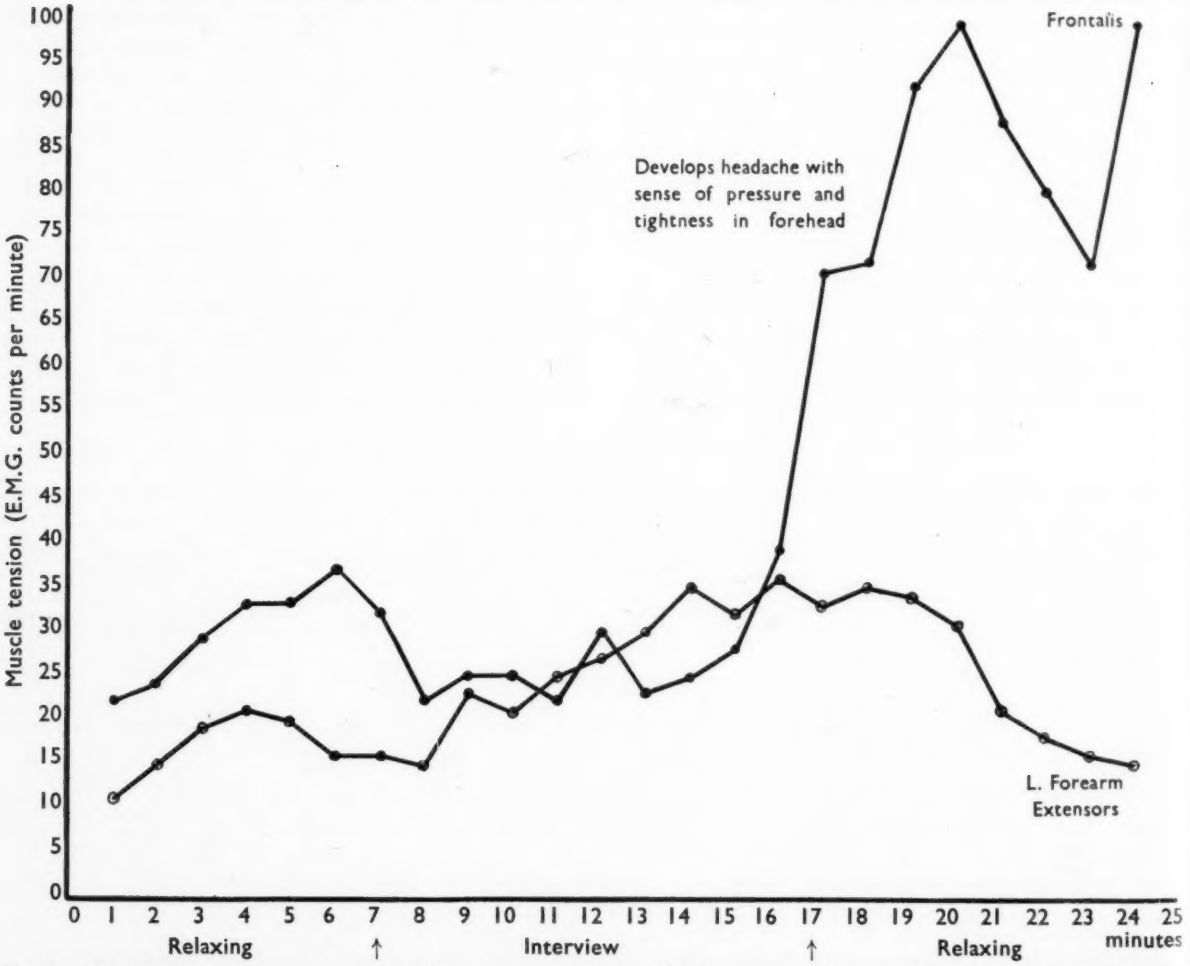

FIG. 3.—G.M.M. (No. 6.) Depression with anxiety. January 26, 1953. The increase in action potentials counted in the frontalis with the onset of headache.

movements, sensations of numbness, etc., and visual disturbances could not be differentiated by our methods from those without these symptoms.

Tendency for Generalized Muscular Tension.—In 15 of the patients muscle tension scores were obtained concurrently from the frontalis, left forearm extensors, extensors of the left foot, and posterior cervical muscles. The scores from these four areas were each placed in rank order and the coefficient of concordance (W) was estimated. The value for W obtained (0·45) was significant at the 5% level. This finding suggests that an increase in bodily tension in one area is reliably associated with an increase in other areas.

Discussion

Malmo and Shagass (1949) had shown that in anxious patients the muscular activity in the neck increased proportionately with the intensity of the stress to which they were exposed (painful stimulation of the forehead) and the increase with stress was greater in the patients than in healthy controls. One of us had found that muscular activity in healthy subjects also increased when they were made anxious by everyday medical procedures such as recording their blood pressures. It has now been found that differences in muscle activity could be observed between anxious patients and healthy controls, even when the subjects were simply relaxing on a bed. Malmo and Shagass had been able to show a difference between their patients and controls only during stress; they concluded that it was the excessive physiological response to stress shown by anxious patients which distinguished them from the normal.

These studies suggest that muscle activity accompanies anxiety. The present investigation carries the quantitative analysis of the relation further. The more the patient experiences tension and anxiety subjectively the higher his muscle tension. This was evident in two well-separated areas, the frontalis and the forearm extensors, which makes it likely that all the voluntary muscles of the body tend to be over-active in these conditions. Three other results support this possibility: (1) the positive correlation ($r = 0{\cdot}45$) between the scores of the patients' feelings of anxiety and the level of muscle activity recorded from the arm and forehead; (2) the significant concordance between the muscle activity in the forehead, neck, arm, and leg; (3) the observations that the patients with the two symptoms most likely to be dependent upon a general increase in muscle tension, starting and tremulousness, had muscle tension scores which were significantly higher than those of control patients without, in both the forearm extensors and the frontalis. It may be concluded that in patients who feel tense and anxious there is a widespread increase in muscle tension. However, we also observed a tendency for the increase in muscle activity to be more evident in some muscle groups than in others: patients with symptoms which they referred to the head, neck, or arms showed a significantly greater muscle tension in these areas. This conclusion is consistent with the earlier findings of Malmo and Shagass (1949b) that psychiatric patients with cardiac complaints upon exposure to stress tend to manifest increased physiological responsiveness in the cardiovascular systems, while those with muscular symptoms respond in the muscular system.

Wolff (1948) reports that some anxious patients who were complaining of headache had a high level of muscle activity in the scalp and neck muscles. We have now confirmed this association in a controlled experiment in which the relation between headache and muscle tension in the frontalis was found to be a significant one. Malmo and Shagass (1949b) had recorded (during stress) more over-activity in the neck muscles of patients with head sensations than in those without. Our procedure, however, avoided the effects produced by movements, such as withdrawing the head from the painful stimulus, so that only muscle tension was scored.

Over-activity in a muscle and the subjective complaint of pain or discomfort in it are closely related. Wolff (1948) and Holmes and Wolff (1952) adduced experimental evidence that the sustained contraction of a muscle, such as occurs in emotionally disturbing situations, if sufficiently prolonged, will give rise to pain in it. If this is the case, then it appears likely that the mechanism underlying some "nervous headaches" is muscular tension, the latter being a part of the physiological changes accompanying the anxiety. Our findings suggest that often other painful muscular symptoms, some of those classed as "fibrositis", for instance, may be similarly produced. Another explanation might be derived from Jacobson's (1938) observation that when attention is concentrated upon a bodily area the number of action potentials increases there; but the responses he recorded were much less than those we were finding. A third alternative might be sought in the familiar tendency for painful areas to be reflexly immobilized by muscular spasm. This could account for the tension in the neck muscles in headache, for example; but it seems improbable that head sensations such as tight bands and

pressure, or feelings of stiffness and discomfort in the arms, would provoke a response of comparable magnitude.

All our patients had been previously judged as tense and anxious by an independent clinical opinion. It was found that the symptoms reported most frequently were of a kind which could be attributed to muscular over-activity. This makes it likely that the recognition of muscle tension is often the observation which prompts the clinician to describe his patients as " tense ". It would make for greater clarity if it were agreed to limit the clinical use of the term to this meaning.

From our findings, as well as those of Wolff (1948), and of Malmo and Shagass (1949a and b), it seems probable that some of the bodily symptoms in anxiety may be attributed to muscular over-activity, the latter being part of the physiological changes accompanying anxiety. Since patients who report feelings of tension have an increased muscular innervation, it is suggested that the feelings of irritability and restlessness of which they often complain may, in fact, be consequences of the massive bombardment of the central nervous system by proprioceptive stimuli arising from the widespread contraction of the voluntary muscles.

Summary

In 30 anxious and tense patients an inventory was made out recording their symptoms, their feelings (anxiety, tension, etc.), and their bodily complaints ascribable to muscular over-activity (head sensations, backache, etc.). The incidence of these complaints was shown.

A direct measure of the muscle tension of these patients was obtained by electronically summing the action potentials in the frontalis, forearm extensors and, in some, the neck muscles, while they relaxed. Reliable scores were obtained.

The patients were divided into two groups: those whose symptom scores on the inventory were above and those who were below the median. The muscle tension scores of the former were significantly higher in both the arms and forehead. Those with the most clinical manifestation of anxiety and tension, therefore, were the more muscularly over-active.

The patients were divided into those with and those without head, neck, or arm symptoms; the former showed significantly higher muscle tension in the relevant muscle. The onset of headache during recordings was accompanied by significant increases in the innervation of the frontalis muscle.

Bodily symptoms attributable to a generalized alteration in muscular innervation, such as tremor and startle, were accompanied by significant increases in muscle activity in well-separated areas.

A significant concordance between four distinct muscle groups suggested that the body musculature as a whole receives increased innervation in patients who are anxious.

References

Cameron, D. E. (1944). *Amer. J. Psychiat.*, **101**, 36.
Holmes, T. H., and Wolff, H. G. (1952). *Psychosomat. Med.*, 14, 18.
Jacobson, E. (1938). *Progressive Relaxation*, 2nd ed., University of Chicago Press.
Malmo, R. B., and Shagass, C. (1949a). *Psychosomat. Med.*, 11, 9.
——, ——(1949b). *Ibid.*, **11**, 25.
Wolff, H. G. (1948). *Headache*, 1st ed., Ch. 17. Oxford University Press, New York.

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AN INTRASPINAL DERMOID CYST ASSOCIATED WITH ANOTHER IN THE OVARY

BY

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Dermoid cysts of the brain are not uncommon, and as many as 200 dermoid and epidermoid cysts found throughout the central nervous system have been reported by Rand and Reeves (1943). However, epidermoid and dermoid tumours of the spinal canal together with teratoid tumours, with or without communicating dermal sinuses, are of extreme rarity. Boldrey and Elvidge (1939) published a total of 43 epidermoid and dermoid cysts of the spinal cord, and in 1946 Ingraham and Bailey reported another five. Sachs and Horrax (1949) listed 59 cases and reported two more of their own, totalling 61 cases. They also published a list of 25 cases of intraspinal teratoids and teratomas, with a brief review of the literature. Moore and Walker (1951) reported a case of intraspinal epidermoid tumour. Sachs and Horrax estimated that the spinal dermoid and epidermoid tumours probably form about a quarter of the total number of those found in the central nervous system. According to Woltman, Kernohan, Adson, and Craig (1951) in their analysis of 979 intraspinal tumours, the spinal dermoid cysts form about 10% of all intraspinal neoplasms.

Case Report

R., a girl aged 19 years, was admitted on June 24, 1952 (Ref. NS 1069), with inability to walk properly, dribbling of urine, and an ulcer in the sole of the left foot.

The complaint started 10 years before with periodic attacks of pain in the small of the back which radiated forwards towards the hip. She found then that she gradually lost power in the left lower limb, which began to waste and also became numb. Six years after the onset of the first symptoms, difficulty in controlling micturition developed. A year later an ulcer developed in the sole of the foot, which persisted for three years.

On examination, she was found to be a well-nourished young girl, who walked with difficulty. The nervous system showed the following abnormalities. Both the lower limbs showed wasting of muscles with loss of power, more marked on the right side in the calf and posterior thigh muscles. The tone was diminished and all the jerks in the lower limbs were lost. There was sensory loss over the buttocks and the posterior aspect of the thighs and legs, and it was more marked on the left side with a pes cavus and perforating ulcer over the left heel. The patient also had occasional dribbling of urine with stress incontinence. Rectal examination showed a lax sphincter.

A clinical diagnosis of a tumour of the cauda equina was made.

On examination of the abdomen, a rounded, firm mass was felt in the hypogastrium, a little to the right side of the midline. The mass was mobile, and was felt to arise out of the pelvis. It did not disappear on catheterization. Though a dumb-bell neurofibroma involving the cauda equina and the retroperitoneal spaces was considered, the mobility of the abdominal tumour excluded this diagnosis. Vaginal examination showed the right fornix to be full while the left was free. The tumour was not felt to be attached to the uterus.

A radiograph of the lumbar spine showed destruction of the pedicles of L2 and L3 vertebrae with concavities

FIG. 1.—Photograph of the spinal cord tumour. A number of tiny cysts are seen towards the periphery.

on the posterior surface of their bodies. Lumbar puncture showed clear cerebrospinal fluid with increased protein (120 mg. per 100 ml.). Cisternal puncture was done and lipiodol injected, and showed a complete block at the level of the second lumbar vertebra.

On July 2, 1952, under general anaesthesia, the spines and laminae of the second and third lumbar vertebrae were removed. The dura was slit longitudinally in the midline and a firm tumour about 2 in. long was revealed. There were some adhesions between the dura and the capsule of the tumour. The tumour was found extending below the laminae of the fourth lumbar vertebra. The incisions were then extended, and the laminae and the spine of the fourth lumbar vertebra removed to expose the tumour completely.

The tumour was elliptical in shape with the narrower end pointing downwards (Fig. 1), and was found to arise from the filum terminale. The growth was carefully lifted off its bed from its lower end and separated from the filaments of the cauda equina. It was severed from its attachment to the cord at its upper end. The dura was stitched up completely and the wound was closed in layers.

The patient had an uneventful post-operative period and began to show signs of gradual improvement in power and control of micturition. The ulcer in the left heel healed after a month.

Pathological Report.—The gross specimen consisted of an ovoid tumour measuring 2 in. × ¾ in. It was capsulated, felt cystic and had a pearly sheen. The cut section presented rather a compact, solid appearance. Careful examination, however, revealed a number of cystic spaces filled with degenerate, amorphous, caseous-like material (Fig. 2). Besides these cystic spaces were sebaceous and sweat glands in a moderately dense collagen stroma. The cysts were lined with stratified squamous epithelium, and some contained amorphous debris similar to that seen in epidermal inclusion cysts. There were no hair follicles.

The solid portions of the tumour presented a compact fibromatous background with interlacing nerve bundles and a few fat cells. In addition, there were elongated pear-shaped or elliptical structures resembling Meissner's corpuscles (Fig. 3).

FIG. 3.—A photomicrograph showing a pear-shaped formation with a coiled-up structure in a neuro-fibrous background with marked resemblance to Meissner's corpuscle. Phosphotungstic acid stain. ×320.

FIG. 2.—Photomicrograph of a number of small cysts; some of them containing structureless debris are seen at the top. A number of glands are grouped below. Van Gieson stain. ×160.

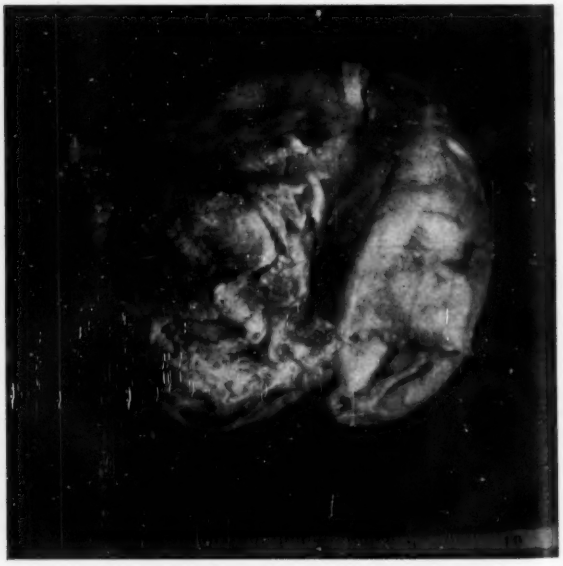

FIG. 4.—The ovarian tumour, which is a cystic globular tumour filled with strands of hair of which the fine strands are not clearly visible in the photograph.

Except for the associated fibrolipomatous tissue background no other mesenchymal structure was found in the several sections studied, neither was there any entodermal representation.

The Ovarian Tumour.—A month later, under general anaesthesia, laparotomy was performed. A spherical tumour, 6 in. in diameter, was found arising from the right ovary. This was removed and the patient had an uneventful post-operative period. It was a large ovoid tumour with a thick, whitish, opaque wall, cystic to the touch (Fig. 4). On opening the cyst, the true nature of the tumour was revealed by an outpouring of pultaceous, greasy, sebaceous material together with abundant strands of hair. The distinctive feature under the microscope was the presence of skin tissue and its appendages in the cyst wall. In addition, there were phagocytic leucocytes and foreign body giant cells in the wall.

No other ectodermal or mesodermal structure was encountered. There was no evidence of malignancy. The tumour was a benign cystic dermoid.

Summary

A case of lumbar intraspinal dermoid cyst associated with another dermoid cyst of the ovary is reported.

From a survey of the available literature, this is the first report of such a case.

Our thanks are due to Col. Sangam Lal, Professor of Surgery, Madras Medical College, who removed the ovarian tumour, and Dr. D. Govinda Reddy, Professor of Pathology, Madras Medical College, and to the Dean, Madras Medical College, for permission to publish this paper.

REFERENCES

Boldrey, E. B., and Elvidge, A. R. (1939). *Ann. Surg.*, **110**, 273.
Ingraham, F. D., and Bailey, O. T. (1946). *J. Neurosurg.*, **3**, 511.
Moore, W. W., and Walker, E. (1951). *Ibid.*, **8**, 343.
Rand, C. W., and Reeves, D. L. (1943). *Arch. Surg., Chicago*, **46**, 350. Quoted by Sachs and Horrax.
Sachs, E., and Horrax, G. (1949). *J. Neurosurg.*, **6**, 97.
Woltman, H. W., Kernohan, J. W., Adson, A. W., and Craig, W. McK. (1951). *Arch. Neurol. Psychiat.*, **65**, 378.

THE MAY (1954) ISSUE

The May (1954) issue contains the following papers :—

Meningiomas within the Lateral Ventricle. A. E. Wall.

Ischaemic Sensory Loss in Patients with Peripheral Nerve Lesions. R. W. Gilliatt and T. Grahame Wilson.

Memory Disturbances in Third Ventricle Tumours. Moyra Williams and Joe Pennybacker.

Variations with Age in the Number of Active Palmar Digital Sweat Glands. Pamela C. B. Mackinnon.

Phosphate Esters in Myotonic Human Muscle. P. C. Caldwell and T. A. J. Prankerd.

A Rare Presenile Dementia Associated with Cortical Blindness (Heidenhain's Syndrome). A. Meyer, Denis Leigh, and C. E. Bagg.

Two Cases of Congenital Atresia of the Foramina of Magendie and Luschka. A. F. J. Maloney.

Autonomic Changes after Unilateral Leucotomy. Alick Elithorn, Malcolm F. Piercy, and Margaret A. Crosskey.

A Comparison of Isoniazid with Modified Insulin Therapy in Neurotic States. Maurice Silverman.

Rapidly Progressive Cerebral Degeneration (Subacute Vascular Encephalopathy) with Mental Disorder, Focal Disturbances, and Myoclonic Epilepsy. D. P. Jones and S. Nevin.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

J. Neurol. Neurosurg. Psychiat., 1954, **17**, 228.

THE PRODUCTION OF GAMMA-GLOBULIN IN THE CENTRAL NERVOUS SYSTEM

BY

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The bulk of the cerebrospinal fluid proteins are by physico-chemical (Booy, 1949, 1950; Kabat, Landow, and Moore, 1942; Kabat, Moore, and Landow, 1942) and immuno-chemical (Kabat, Glusman, and Knaub, 1948; Kabat, Freedman, Murray, and Knaub, 1950) criteria identical with the serum proteins. Apart, however, from being present in considerably lower total concentration the various components do not occur in the same proportions in the cerebrospinal fluid and in the serum. Albumin is preponderant in the cerebrospinal fluid and α- and β-globulins are present in amounts which may in normal subjects be too low to be detected. Alterations are found both in the total protein concentration of the cerebrospinal fluid and in the relative concentrations of the components in disease affecting the central nervous system. Bing and Neel (1942) have reviewed the earlier studies on albumin/globulin ratios obtained by salting-out techniques. These indicated a relative increase in the globulin fraction in chronic inflammatory diseases such as disseminated sclerosis and neurosyphilis. More detailed electrophoretic and immuno-chemical studies have shown that the increase in this fraction is due to γ-globulin.

Bing and Neel (1942) also pointed out that a characteristic feature of the lesions in these diseases is the accumulation of plasma cells in the central nervous system. Since the production of γ-globulin appears to be a function of the reticulo-endothelial system, in particular of plasma cells, and since antibodies are associated with γ-globulin (see review by Burnet and Fenner, 1949) it would be of interest to ascertain the extent, if any, to which the γ-globulins in the cerebrospinal fluid are produced in the central nervous system. That antibodies may be produced there has been suggested by clinical observations that positive Wassermann reactions may be found in the cerebrospinal fluid when the reactions in the serum are negative and, recently, by the demonstration in monkeys of the production of antibody to poliomyelitis virus within the central nervous system (Morgan, 1947a and b; Morgan, Howe and Bodian, 1947).

This paper describes the results of electrophoretic studies on the protein components of cerebrospinal fluids and sera in selected pathological conditions. The findings suggest that a proportion of the γ-globulin of the cerebrospinal fluid can be produced in the central nervous system.

Experimental

Principles.—The relative permeability of the blood-cerebrospinal fluid barrier to different serum proteins was investigated by comparing their concentrations in the serum and in the cerebrospinal fluid in three patients with multiple myeloma whose serum γ-globulin level was grossly raised. Four normal controls, 26 cases of disseminated sclerosis, and two of neurosyphilis were similarly investigated in order to determine whether (*a*) the concentrations of different protein components in the cerebrospinal fluid vary independently, and (*b*) the proportion of γ-globulin in these diseases is significantly higher than would be expected from a study of the cases of multiple myeloma.

Lastly, four normal, Mantoux-positive subjects who had received intrathecal tuberculin were investigated. The reaction evoked comprises two phases, both associated with an increase in the cell count and protein content of the cerebrospinal fluid. The first phase, in which the cells are largely polymorphonuclear, reaches a maximum in 24 hours, and is followed by a short remission. In the second phase, which reaches a maximum between the fourth and seventh day and is more prolonged, the cells are lymphocytes. It was thus possible in these subjects to follow the changes from an acute to a chronic stage. These studies were conducted as part of the work on tuberculous meningitis described by Swithinbank, Smith, and Vollum (1953).

Methods.—Total protein concentrations of all sera and of the cerebrospinal fluids from the subjects receiving intrathecal tuberculin were determined refractometrically. Those of the remaining cerebrospinal fluids were determined turbidometrically (to the nearest 5 mg./100 ml.) or by a modified micro-Kjeldahl technique.

Protein analyses were performed electrophoretically in phosphate buffers of *p*H. 8·0. The concentrations of the buffers were such that approximately the same protein/buffer ratio was always obtained, since this ratio affects to some extent the analytical results (Perlmann and Kaufman, 1945). Thus, the buffer concentrations were M/15 for sera, M/30 for cerebrospinal fluids from the cases receiving intrathecal tuberculin, and M/60 for all other cerebrospinal fluids.

Sera were diluted 1 in 6 with buffer and dialysed against further volumes of buffer. Cerebrospinal fluids, about 20 ml. from each patient, were first dialysed against buffer in order to eliminate non-protein nitrogen and to introduce buffer. They were then concentrated to approximately one fifth (for the cases of intrathecal tuberculin) or one tenth of their original volumes (for all other cases) by dialysing against 50% gum arabic solution (Ewerbeck, 1950) and finally redialysed against buffer. With each fluid all these operations were carried out in the same dialysis bag, at 0 to 5° C. This has the advantage over methods depending on evaporation or ultra-filtration in that changes due to denaturation and adsorption on surfaces are reduced to a minimum.

Electrophoresis was carried out in the Tiselius (1937) apparatus, employing the diagonal Schlieren and cylindrical lens optical system. Measurements of areas were obtained from tracings of enlargements of the photographed patterns. With cerebrospinal fluids of low protein content a preliminary photograph, with the same exposure and magnification, was taken immediately on forming the boundaries in order to correct for base-line distortion at high magnification. Values for the negative (descending) limb only were used in the analyses of results since it was often found with cerebrospinal fluids that the δ-boundary in the ascending limb was not sufficiently separated from the γ-globulin boundary.

Results

Multiple Myeloma.—The results of the three cases investigated are shown in Table I. On comparing the albumin/γ-globulin ratio of the serum with that of the cerebrospinal fluid (R_s/R_c value in the table), it will be seen that the blood-cerebrospinal fluid barrier was respectively 0·27, 0·23, and 0·43 times as permeable to γ-globulin as to albumin if it is assumed that both components were derived predominantly from the serum.

TABLE I

CEREBROSPINAL FLUID AND SERUM PROTEIN COMPONENTS IN MULTIPLE MYELOMA

Case	Total Protein (g./100 ml.)	Protein Fractions as % of Total Proteins			Albumin/γ-Globulin	R_s/R_c†
		Albumin	(α + β)-Globulin	γ-Globulin		
26	0·045	47·9	15·4	36·7	1·3	0·27
	*10·6**	*23·0*	*10·8*	*66·2*	*0·35*	
44	0·048	39·3	12·8	42·9	0·91	0·23
	14·2	*16·7*	*4·5*	*78·9*	*0·21*	
45	0·051	72·0	5·9	14·7	4·9	0·43
	7·5	*51·5*	*21·8*	*24·5*	*2·1*	

*Serum concentrations in italics.
†R_s and R_c are albumin/γ-globulin ratios of the serum and cerebrospinal fluid respectively.

Controls, Disseminated Sclerosis, and Neurosyphilis.—In Table II cases of disseminated sclerosis and neurosyphilis are presented in groups according to the total amount of protein found in the cerebrospinal fluid. This table shows that R_s/R_c values are considerably increased at the higher total protein concentrations.

In Fig. 1 the cerebrospinal fluid concentrations of (α+β)-globulin and of γ-globulin have been plotted against those of albumin. There is a discernible tendency for a linear relationship between albumin and (α+β)-globulin (correlation coefficient 0·76) but this relationship is less noticeable between

TABLE II

CEREBROSPINAL FLUID AND SERUM PROTEIN COMPONENTS IN DISSEMINATED SCLEROSIS, NEUROSYPHILIS, AND CONTROLS

Group	Diagnosis	Cerebrospinal Fluids						Sera					R_s/R_c
		No. of Cases	Total Protein (mg./100 ml.)	Albumin (mg./100 ml.)	α + β Globulin (mg./100 ml.)	γ-Globulin (mg./100 ml.)	Albumin/γ-Globulin (mg./100 ml.)	Total Protein (g./100 ml.)	Albumin (g./100 ml.)	α + β Globulin (g./100 ml.)	γ-Globulin (g./100 ml.)	Albumin/γ-Globulin (g./100 ml.)	
1	Controls	4	25–30·4	17·9±2·4	4·5±1·6	3·7±1·3	6·2±4·0	7·91±0·41	4·65±0·37	2·15±0·58	1·11±0·22	4·2±1·0	0·87±0·36
2	Disseminated sclerosis	5	15–25	14·1±2·9	3·0±1·6	3·9±0·9	3·9±1·5	7·43±0·35	4·50±0·59	1·60±0·27	1·53±0·20	3·9±1·8	0·98±0·24
3	Disseminated sclerosis	10	25·1–35	18·8±3·6	4·0±1·2	5·8±1·5	3·9±0·97	7·26±0·81	4·58±0·49	1·62±0·26	1·12±0·29	4·3±0·9	1·23±0·59
4	Disseminated sclerosis	5	35·1–50	26·7±4·5	5·9±1·3	12·4±3·1	2·4±1·0	7·64±1·23	4·89±0·53	1·53±0·41	1·22±0·37	4·5±1·7	2·06±0·54
5	Disseminated sclerosis and neurosyphilis	5	50·1–65	36·7±6·3	8·5±2·3	13·8±5·8	3·3±1·7	7·25±0·55	4·27±0·24	1·48±0·27	1·51±0·62	3·2±1·0	1·16±0·51
6	Disseminated sclerosis and neurosyphilis	3	65·1–80	45·2±1·6	10·9±0·7	17·4±5·4	2·9±0·74	7·27±0·88	4·59±0·68	1·60±0·11	1·07±0·14	4·3±0·5	1·68±0·60

albumin and γ-globulin concentrations (correlation coefficient 0·56).

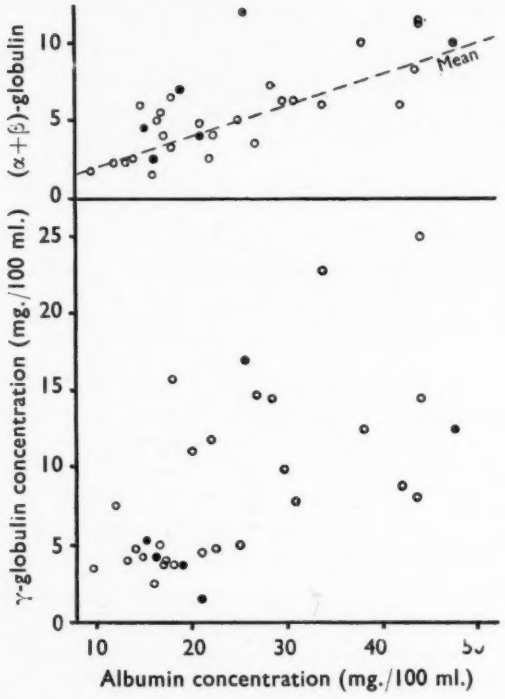

FIG. 1.—Cerebrospinal fluid albumin concentrations plotted against (α + β)-globulin (above) and γ-globulin concentrations (below). Black circles represent normal controls; clear circles, disseminated sclerosis; dotted circles, neurosyphilis.

Intrathecal Tuberculin.—Fig. 2 shows changes in the globulin components of the cerebrospinal fluid and of the serum in one subject over a period of three weeks. The globulin concentrations are expressed as a percentage of albumin rather than of total protein, since the cerebrospinal fluid albumin level is probably a better criterion of the permeability of the blood-cerebrospinal fluid barrier. The variations in the concentration of total protein are also given (heavy line) on a different scale in order to indicate the phases of the reaction.

The usual diphasic response in the total protein appears in each case, but in addition there is a consistent tendency for the γ-globulin/albumin ratio to rise during the second half of the first week coinciding with the "lymphocytic" second phase. From Fig. 2 it can be seen that these changes in the cerebrospinal fluid are not related to those in the serum. Of interest is the γ-globulin "spike" shown in Fig. 2 on the third day. This subject had received intrathecal tuberculin on a previous occasion and this reaction is reminiscent of an anamnestic response.

Discussion

It is remarkable that the correlation coefficient for cerebrospinal fluid (α+β)-globulin and albumin concentrations (shown in Fig. 1) should be so high despite the errors of estimation at such low globulin concentrations, and the fact that the concentration of a protein in the cerebrospinal fluid depends to some extent on its concentration in the serum and that the relative permeability of the blood-cerebrospinal fluid barrier to the different proteins may vary from individual to individual. Since (α+β)-globulin in the cerebrospinal fluid showed a greater tendency to vary in parallel with albumin than did γ-globulin, the conclusion may be drawn that the first two classes of protein have a common source, that is, both being derived from the serum, while a proportion at least of the γ-globulin originates independently within the central nervous system.

This conclusion gains support from the following additional considerations. The mean value for the cerebrospinal fluid/serum γ-globulin ratio in the cases of disseminated sclerosis and of neurosyphilis was found to be 1·4 times this ratio for albumin. Moreover, this figure was significantly higher for the cases with total proteins over 35 mg./100 ml. ($R_s/R_c = 1{\cdot}62 \pm 0{\cdot}67$) than for those with lower total protein concentrations ($R_s/R_c = 1{\cdot}15 \pm 0{\cdot}51$), despite the possibility that the electrophoretic technique may give falsely high values for γ-globulin at very low concentrations. If these figures are compared with those obtained in the cases of multiple myeloma ($R_s/R_c = 0{\cdot}27$, 0·23, and 0·43), it is evident either that the permeability of the blood-cerebrospinal fluid barrier is grossly disturbed in disseminated sclerosis and neurosyphilis, or that some γ-globulin is produced in the central nervous system in these diseases. It would, however, be difficult to explain how a simple increase in permeability of the blood-cerebrospinal fluid barrier could result in greater permeability to the γ-globulin than to the smaller albumin molecule.

Two of the patients with disseminated sclerosis had high serum antistreptolytic O titres (480 and 700 respectively). It could be calculated from the corresponding cerebrospinal fluid serum γ-globulin ratios, that, were all cerebrospinal fluid γ-globulin derived from the serum, the antibody should have been detectable in the cerebrospinal fluid. None, however, could be detected in either case. Similar findings on the distribution of *Brucella* agglutinins have been reported by Spink and Kimball (1950).

In the subjects receiving intrathecal tuberculin the γ-globulin/albumin ratio again varied more than did the β-globulin/albumin ratio. (α-globulins

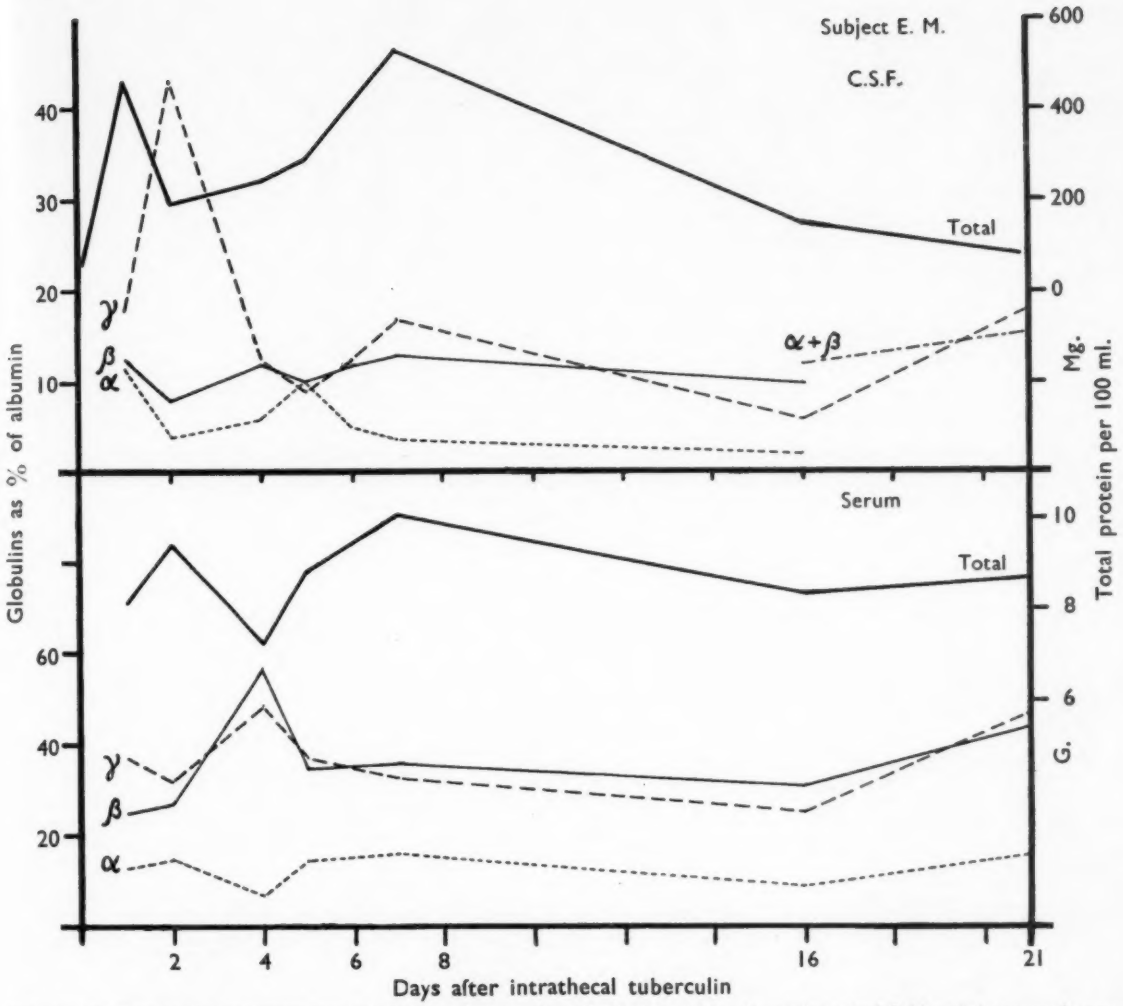

FIG. 2.—Changes in the concentrations of globulins (expressed as % of albumin) in the cerebrospinal fluid and the serum in one subject following intrathecal tuberculin over a period of three weeks. Changes in the total proteins (heavy lines, plotted to scale at right) are also shown in order to indicate the phases of the reaction.

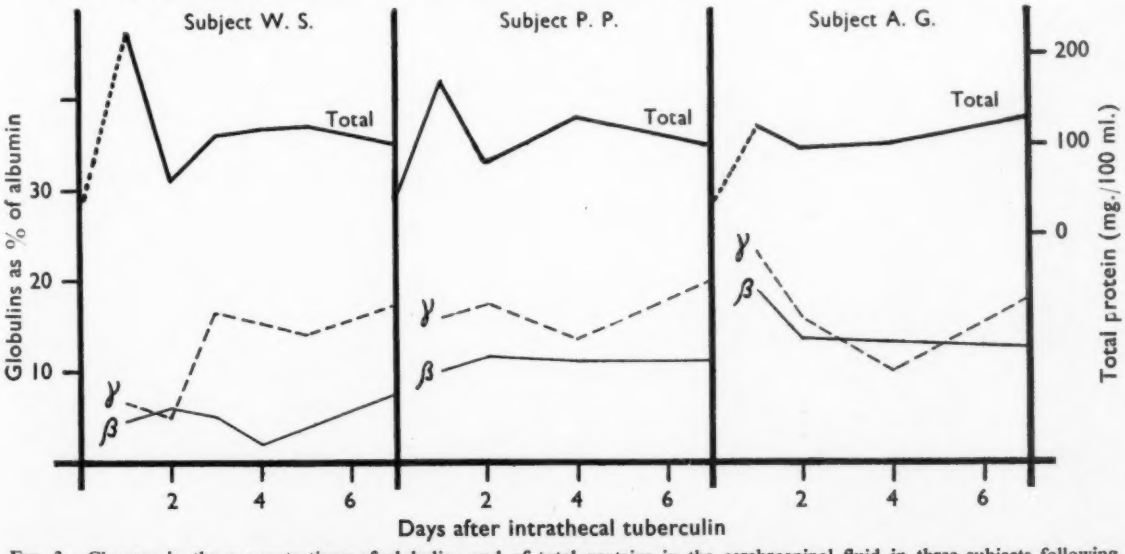

FIG. 3.—Changes in the concentrations of globulins and of total proteins in the cerebrospinal fluid in three subjects following intrathecal tuberculin, over a period of one week each.

in the subjects shown in Fig. 3 were too low for useful inclusion.) The difference in the degrees of variation was significant at the 12% level of probability by the t-test which was applied to the mean difference between standard deviations of the two ratios computed for each of the four subjects. Hence, though not by themselves conclusive, these findings support the conclusions derived from the studies on disseminated sclerosis and neurosyphilis.

In 19 of the patients with disseminated sclerosis in whom lymphocyte counts of the cerebrospinal fluid were performed, the γ-globulin/albumin ratio was significantly higher if the cells numbered 2 or more per ml. (mean ratio $=4{\cdot}1 \pm{\cdot}9$) than in the remainder (mean ratio $=2{\cdot}8 \pm 1{\cdot}2$). The rise in the proportion of γ-globulin in the cerebrospinal fluid in the cases receiving intrathecal tuberculin also appeared during the phase which was characterized by a high cerebrospinal fluid lymphocyte count. Since the production of γ-globulin in the body is associated with the reticulo-endothelial system, these findings suggest that the accumulations of lymphoid tissue in the central nervous system may be the source of the locally produced γ-globulin.

Summary

The cerebrospinal fluid and serum proteins have been studied electrophoretically in four normal controls, three cases of multiple myeloma, 26 of disseminated sclerosis, and two of neurosyphilis, and in four normal Mantoux-positive subjects receiving intrathecal tuberculin.

In chronic inflammatory disease of the central nervous system the γ-globulin/albumin ratio of the cerebrospinal fluid was found to be higher than that of the serum, and varied more than did the $(\alpha+\beta)$-globulin/albumin ratio.

It was concluded that in these diseases a proportion of the cerebrospinal fluid γ-globulin was produced in the central nervous system.

A rise in γ-globulin was found to be associated with a raised lymphocyte count in the cerebrospinal fluid.

I wish to express my gratitude to Professor E. C. Dodds, F.R.S., and to Mr. J. R. P. O'Brien for their support in this work, to Dr. D. McAlpine, under whose programme of disseminated sclerosis research part of the work was undertaken, to Dr. Honor Smith, and to Dr. Nigel Compston. Thanks are also due to Professor R. W. Scarff for data on antistreptolytic titres and cerebrospinal fluid lymphocyte counts.

References

Bing, J., and Neel, A. V. (1942). *Acta med. scand.*, **111**, 57.
Booy, J. (1949). *Folia psychiat., Amst.*, **52**, 247.
—— (1950). *Ibid.*, **53**, 502.
Burnet, F. M., and Fenner, F. (1949). *The Production of Antibodies*, 2nd ed. Macmillan, London.
Ewerbeck, H. (1950). *Klin. Wschr.*, **28**, 692.
Kabat, E. A., Freedman, D. A., Murray, J. P., and Knaub, V. (1950). *Amer. J. med. Sci.*, **219**, 55.
——, Glusman, M., and Knaub, V. (1948). *Amer. J. Med.*, **4**, 653.
——, Landow, H., and Moore, D. H. (1942). *Proc. Soc. exp. Biol., N.Y.*, **49**, 260.
——, Moore, D. H., and Landow, H. (1942). *J. clin. Invest.*, **21**, 571.
Morgan, I. M. (1947a). *J. exp. Med.*, **85**, 131.
—— (1947b). *Amer. J. Hyg.*, **45**, 390.
——, Howe, H. A., and Bodian, D. (1947). *Ibid.*, **45**, 379.
Perlmann, G. E., and Kaufman, D. (1945). *J. Amer. chem. Soc.*, **67**, 638.
Spink, W. W., and Kimball, A. (1950). *Proc. Soc. exp. Biol., N.Y.*, **73**, 67.
Swithinbank, J., Smith, H. V., and Vollum, R. L. (1953). *J. Path. Bact.*, **65**, 565.
Tiselius, A. (1937). *Trans. Faraday Soc.*, **33**, 524.

BOOK REVIEWS

Diagnosis and Localisation of Brain Tumours. By George E. Moore. (Pp. xxiii + 217 + index; 66 figures, 6 colour plates. 75*s.* 6*d.*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1953.

This monograph gives a detailed account of fluorescent and other dyes, and of radioactive tracers, in the diagnosis and localization of brain tumours. After a brief survey of the blood-brain barrier controversy, the use of fluorescein given by intravenous injection is described at length. Included are full details of the procedure, and of the results obtained in clinical practice with different types of tumour, and in patients with epileptic foci. Among many features of interest are the observation that the application of a coagulating current to the external surface of the dura causes sufficient damage to the underlying cortex to cause it to fluoresce, and the curious finding that meningiomas do not always show much fluorescence although, since their blood supply comes largely from vessels which "are not considered to have the blood-brain-barrier mechanism", they should invariably fluoresce well.

A short chapter describes the use of highly coloured dyes for similar purposes, but concludes that their clinical use, while theoretically feasible, is not practical, owing to the somewhat prolonged and intense discoloration of the patient.

Studies with radio-opaque substances are described briefly, and the author does not find them suitable for the diagnosis of brain tumours. The next 80 pages describe the use of the radioactive tracers for the localization of brain tumours, and include useful studies of the problems involved and of the clinical results obtained. This method appears of very real use, the chief substances recommended being radioactive di-iodofluorescein and radioactive iodinated human serum albumin. With the latter substance a dose of 450 microcuries of I^{131} is said to give counting rates of about 10,000 per minute over the skull when using a scintillation counter. The use of radioactive potassium iodide KI^{131} was also tried in 10 patients with brain tumours, and found to give excellent results. As a precaution the thyroid was "blocked" by prior administration of Lugol's solution.

Later chapters describe experimental brain tumours in inbred mice, and some useful studies on the blood-brain barrier.

The six colour plates are well chosen, and add greatly to the value of the book. The work is written from a practical and experimental standpoint, and should be of much value to neurosurgeons and research workers wishing to use the techniques described. It includes many useful practical details, and has the admirable feature of describing the difficulties and drawbacks of the various procedures as well as their merits. The book is clearly written and well produced, but not inexpensive. It was given the quinquennial S. D. Gross Award for 1950 by the Philadelphia Academy of Surgery.

Manic-Depressive Disease. By John D. Campbell. (Pp. 403. 55*s.*) Philadelphia: J. B. Lippincott Company. 1953.

This is a clinician's monograph based mainly on a detailed study of 522 patients suffering from manic-depressive illness in various forms and phases. The author gives excellent clinical descriptions and emphasizes especially the way in which the essential symptoms of cyclothymia may be discerned in the diverse presenting syndromes which are seen as frequently by the general practitioner as by the psychiatrist. In the field of clinical description and treatment the author is on sure ground; but he goes farther and elaborates a hypothesis to the effect that manic-depressive illness is fundamentally a disturbance of the autonomic nervous system. He enumerates 29 symptoms which he regards as evidence of such a disturbance, and he finds that in 82% of his patients various combinations of these predominate over the psychic symptomatology. There is much room for debate about the cause-effect relationship of these groups of symptoms, and not all readers will be convinced that it is quite as simple or as clear-cut as the author suggests. Nevertheless, his ideas are stimulating and should certainly give grounds for reflexion to those who are excessively preoccupied with psychodynamics in this illness.

There are good accounts of the history of the delineation of manic-depressive illness and of the approach to its problems by various schools of thought. References and the index are adequate. The style is pleasant and easy and although the book will be as valuable to the general physician as to the psychiatrist, it could serve its purpose best if it were studied against a background of wider psychiatric reading.

Progress in Neurology and Psychiatry, Vol. VIII. Edited by E. A. Spiegel. (Pp. 604. 70*s.*; $10.00.) London: George Allen and Unwin; New York: Grune and Stratton. 1953.

This book is intended to summarize recent work in the neuropsychiatric field, and has been compiled by 81 authors. There is a minimum of discussion, for the book is largely composed of summaries of the principal papers on each subject with only enough comment to lead from one paper to the next. Some authors, commendably anxious to be brief become almost telegraphic, or say, for instance, "The sometimes acrimonious discussion on the sheath as a barrier . . . seems to be settled by the work of . . ." and tantalizingly refrain from telling us in what way it has been settled.

With so many authors covering so wide a field the standard and style are bound to vary, but the average level is very satisfactory.

Gehirn und Auge. By Robert Bing and Roland Brückner. (Pp. 248. Sw. fr. 14.) Basle : Benno Schwabe. 1954.

This is a new edition of a well-known book which, when first published 40 years ago, must have been thoroughly up to date. Many chapters are still most helpful to the student, and there is an excellent account of many aspects of the anatomy, physiology, and pathology of the visual apparatus. From the neurologist's point of view, however, the book is disappointing. The recent work on supra-calcarine visual disorders is entirely ignored and indeed the important studies of Morris Bender (New York) and of Eberhard Bay (Heidelberg) are not even mentioned.

The illustrations of retinal disorders and of disturbance of ocular movements are few and are technically below present-day standards. Many well-known conditions, such as myasthenia gravis, traumatic lesions of the optic chiasma, wounds of the calcarine area, aneurysms of the cerebral arteries, central ocular palsies in poliomyelitis, muscular dystrophy affecting the ocular muscles, and hysterical disorders of vision and eye movements are inadequately considered

Besinnung und Bewusstsein. By G. E. Störring. (Pp. 134 ; DM. 11.–) Stuttgart : Georg Thieme. 1953.

The sub-title of this work might be translated as " Organization and Disorganization of the Personality from the Psychological, Paedagogical, Sociological, and Psychiatric Viewpoint ". The theme of the study is " Besinnung," which may be literally translated as reflexion or deliberation, but is given a special meaning by the author. It is, in his conception, a superior psychic function, a state of self-reflexion, contemplation, and detachment all in one. This state, in which the personality takes account of itself, recollects and integrates past life, and formulates values for the future, is liable to interference from various sides. It is not attempted, for instance, by the unstable or the callous psychopath ; it is disturbed or distorted in schizophrenia ; and it is impossible of attainment in the case of some structural lesions of the brain, such as frontal tumour. The author believes that " Besinnung " is an important factor in the normal development of the child and adolescent. He criticizes modern mechanistic philosophies which neglect the value of contemplation and self-reflexion.

BOOKS RECEIVED

(Review in a later isssue is not precluded by notice here of books recently received.)

Traité Technique de Tomographie Osseuse. By Robert Herdner ; Foreword by Prof. D. Petit-Dutaillis. (Pp. 408 ; 338 figures. Fr.frs. 4,600.-) Paris : Masson et Cie. 1953.

Neurosurgery of Infancy and Childhood. By Franc D. Ingraham and Donald D. Matson. (Pp. 456 ; 482 figures. £5 7*s.* 6*d.*) Oxford : Blackwell Scientific Publications ; Springfield, Illinois : Charles C. Thomas.

Frontal Lobes and Schizophrenia. Edited by Milton Greenblatt and Harry C. Solomon. (Pp. xi + 425 ; 35 figures. £4 10*s.*) London : Lange, Maxwell & Springer ; New York : Springer Publishing Company. 1953.

The Mentally Subnormal Child. W.H.O. Technical Report Series No. 75. (Pp. 46. 1*s.* 9*d.*) London : H.M. Stationery Office ; Geneva : World Health Organization. 1954.

The Painful Phantom : Psychology, Physiology and Treatment. Monograph by Lawrence C. Kolb. (Pp. 50. 11*s.*) Oxford : Blackwell Scientific Publications ; Springfield, Illinois : Charles C. Thomas. 1954.

The Basis of Clinical Neurology. By Samuel Brock. 3rd edition. (Pp. xii + 510 ; 124 figures. 54*s.*) London : Baillière, Tindall & Cox. 1953.

The Self in Psychotic Process : Its Symbolization in Schizophrenia. By John Weir Perry ; Foreword by C. G. Jung. (Pp. 184. 37*s.* 6*d.*) London : Cambridge University Press ; Berkeley and Los Angeles : University of California Press. 1953.

The Six Schizophrenias : Reaction Patterns in Children and Adults. By Samuel J. Beck ; with a Clinical Introduction by Roy R. Grinker and a chapter concerning Q Methodology by Professor William Stephenson. (Pp. 238. $5.00) New York : American Orthopsychiatric Association. 1954.

Recent Developments in Psychosomatic Medicine. Edited by Eric D. Wittkower and R. A. Cleghorn. 1st edition. (Pp. 495. 50*s.*) London : Sir Isaac Pitman. 1954.

Voies et Centres Nerveux. Introduction systématique à la neurologie. By J. Delmas and A. Delmas. 4th edition, revised. (Pp. 218 ; 143 figures. Fr.frs. 1,150.-) Paris : Masson et Cie. 1954.

ANNOUNCEMENTS

Symposium Neuroradiologicum

The fourth Symposium Neuroradiologicum will be held in London from September 13 to 17, 1955.

Radiologists, neurosurgeons, neurologists, and others interested will be most welcome. All wishing to contribute papers are invited to communicate as soon as possible with the Honorary Secretary, Dr. R. D. Hoare, at the National Hospital, Queen Square, London, W.C.1.

Sixth Latin-American Neurosurgical Congress

The sixth Latin-American Neurosurgical Congress (Secretary-General Dr. R. Arana-Iniguez, Convencion 1287, Montevideo) will be held in Montevideo from March 21 to 24, 1955, together with the 2nd South-American Electroencephalographical Congress (Secretary-General, Dr. P. Pinto Pupo, San Pablo, Brazil). Intending visitors should apply before October 1, 1954.